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(71) Applicant: Kissei Pharmaceutical Co., Ltd.
Matsumoto-City Nagano-Pref. 399-8710 (JP)

(72) Inventors:

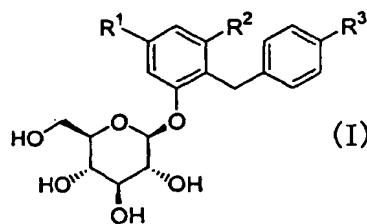
- FUJIKURA, Hideki
Shimauchi
Matsumoto-shi, Nagano 390-0851 (JP)
- NISHIMURA, Toshihiro
Minamiazumi-gun, Nagano 399-8304 (JP)

- FUSHIMI, Nobuhiko
Matsumoto-shi, Nagano 390-0313 (JP)
- TATANI, Kazuya
Matsumoto-shi, Nagano 390-0805 (JP)
- KIKUCHI, Norihiko
Matsumoto-shi, Nagano 390-1242 (JP)
- KATSUNO, Kenji
Kamiina-gun, Nagano 399-0601 (JP)
- ISAJI, Masayuki
Shiojiri-shi, Nagano 399-0704 (JP)

(74) Representative: Hayes, Adrian Chetwynd et al
Boult Wade Tennant,
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT (GB)

(54) **GLUCOPYRANOSYLOXYBENZYL BENZENE DERIVATIVES, MEDICINAL COMPOSITIONS
CONTAINING THE SAME AND INTERMEDIATES IN THE PRODUCTION THEREOF**

(57) The present invention relates to glucopyranosyloxybenzylbenzene derivatives represented by the general formula:



wherein R¹ represents a hydrogen atom, a hydroxy group, a substituted or unsubstituted amino group, a carbamoyl group, a substituted or unsubstituted(lower alkyl) group, a substituted or unsubstituted(lower alkoxy) group etc.; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a substituted or unsubstituted(lower alkyl) group, a substituted or unsubstituted(lower alkoxy) group, a substituted or unsubstituted(lower alkylthio) group etc., or pharmaceutically acceptable salts thereof, which have an inhibitory activity in human SGLT2 and are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complication or obesity, pharmaceutical compositions comprising the same and intermediates thereof.

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Description**Technical Field**

- 5 [0001] The present invention relates to glucopyranosyloxybenzylbenzene derivatives or pharmaceutically acceptable salts thereof, which are useful as medicaments, pharmaceutical compositions comprising the same and intermediates thereof.
- [0002] More particularly, the present invention relates to glucopyranosyloxybenzylbenzene derivatives or pharmaceutically acceptable salts thereof, which have an inhibitory activity in human SGLT2 and are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complication or obesity, pharmaceutical compositions comprising the same and intermediates thereof.

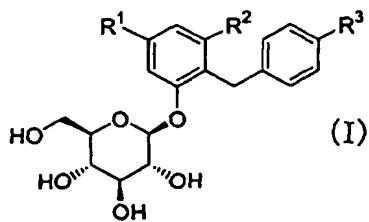
Background Art

- 15 [0003] Diabetes is a lifestyle-related disease with the background of change of eating habits and lack of exercise. Hence, diet and exercise therapies are performed in patients with diabetes. Furthermore, when sufficient control and continuous therapies are difficult, drug treatment is simultaneously performed. Now, biguanides, sulfonylureas and agents for reducing insulin resistance have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglycemia, respectively. In the case of using
20 agents for reducing insulin resistance, adverse effects such as edema occasionally are observed, and it is also implicated in advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.
- [0004] In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 (Na^+ /glucose cotransporter 2) is present
25 in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose, at the kidney, subsequently promotes excretion of excess glucose through the urine, and normalizes blood glucose level. Therefore, fast development of antidiabetic agents, which have a potent inhibitory
30 activity in human SGLT2 and have a new mechanism, has been desired. Furthermore, since such agents promote the excretion of excess glucose through the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventative effect on obesity.

Disclosure of the Invention

- 35 [0005] The present inventors have studied earnestly to find compounds having an inhibitory activity in human SGLT2. As a result, it was found that certain glucopyranosyloxybenzylbenzene derivatives show an excellent inhibitory activity in human SGLT2 as mentioned below, thereby forming the basis of the present invention.
- [0006] The present invention is to provide the following glucopyranosyloxybenzylbenzene derivatives and pharmaceutically acceptable salts thereof, which exert an inhibitory activity in human SGLT2 and show an excellent hypoglycemic effect by excreting excess glucose in the urine through preventing the reabsorption of excess glucose at the kidney, and pharmaceutical compositions comprising the same.
- [0007] Thus, the present invention relates to a glucopyranosyloxybenzylbenzene derivative represented by the general formula:

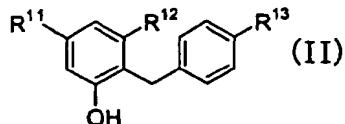
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wherein R¹ represents a hydrogen atom, a hydroxy group, an amino group, a mono or di(lower alkyl) amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a hydroxy (lower alkyl) group, a hydroxy (lower alkoxy) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl

- (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio-group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a lower alkenyloxy group, an aralkyloxy group, a hydroxy(lower alkenyl) group, a carboxy group, a lower alkoxy carbonyl group, a cyano group, an aralkyloxy(lower alkyl) group, a cyano (lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di(lower alkyl)amino group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; with the proviso that R³ does not represent a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group or a lower alkoxy-substituted (lower alkylthio) group when R¹ represents a hydrogen atom or a hydroxy (lower alkyl) group and R² represents a hydrogen atom, or a pharmaceutically acceptable salt thereof.
- [0008] The present invention relates to a pharmaceutical composition comprising as an active ingredient a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.
- [0009] The present invention relates to a human SGLT2 inhibitor comprising as an active ingredient a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.
- [0010] The present invention relates to an agent for the prevention or treatment of a disease associated with hyperglycemia, which comprises as an active ingredient a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.
- [0011] The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effect amount of a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.
- [0012] The present invention relates to a use of a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.
- [0013] In addition, the present invention relates to a benzylphenol derivative represented by the general formula:

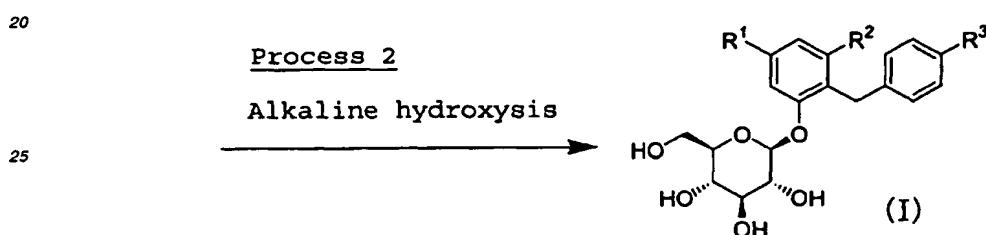
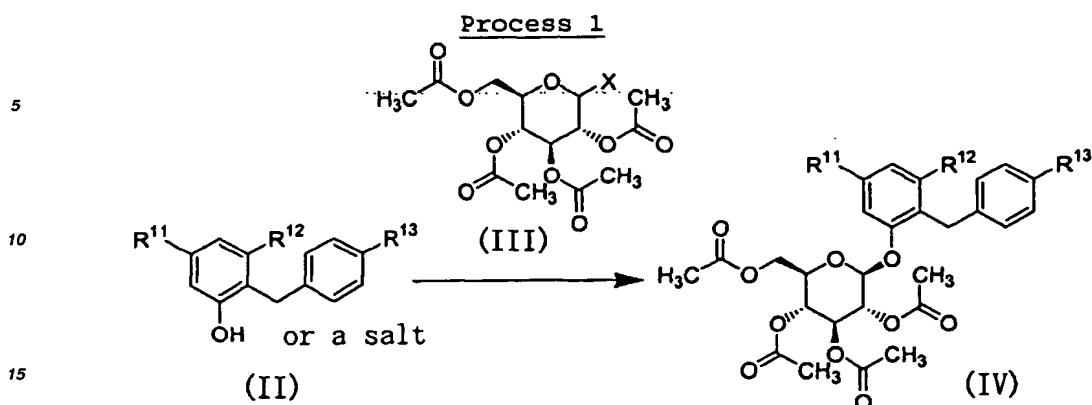


- wherein R¹¹ represents a hydrogen atom, a protected hydroxy group, a protected amino group, a protected mono(lower alkyl)amino group, a di (lower alkyl) amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a protected hydroxy(lower alkyl) group, a protected hydroxy(lower alkoxy) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; R¹² represents a hydrogen atom or a lower alkyl group; and R¹³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a protected hydroxy(lower alkyl) group, a protected hydroxy(lower alkoxy) group, a protected hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkylthio group, a lower alkenyloxy group, an aralkyloxy group, a protected hydroxy(lower alkenyl) group, a carboxy group, a lower alkoxy carbonyl group, a cyano group, an aralkyloxy(lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, a protected amino group, a protected mono(lower alkyl)amino group, a di(lower alkyl)amino group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; with the proviso that R¹³ does not represent a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a protected hydroxy (lower alkyl) group, a protected hydroxy(lower alkoxy) group, a protected hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group or a lower alkoxy-substituted (lower alkylthio) group when R¹¹ represents a hydrogen atom or a protected hydroxy(lower alkyl) group and R¹² represents a hydrogen atom, or a salt thereof.
- [0014] In the present invention, the term "lower alkyl group" means a straight-chained or branched alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an

isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a hexyl group or the like; the term "lower alkoxy group" means a straight-chained or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, an isopentyloxy group, a neopenetyloxy group, a tert-pentyloxy group, a hexyloxy group or the like; and the term "lower alkylthio group" means a straight-chained or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a sec-butylthio group, a tert-butylthio group, a pentylthio group, an isopentylthio group, a neopenetylthio group, a tert-pentylthio group, a hexylthio group or the like. The term "hydroxy(lower alkyl) group" means a straight-chained or branched hydroxylalkyl group having 1 to 6 carbon atoms such as a hydroxymethyl group, a 2-hydroxyethyl group, a 1-hydroxyethyl group, a 3-hydroxypropyl group, a 2-hydroxypropyl group, a 1-hydroxypropyl group, a 2-hydroxy-1-methylethyl group, a 4-hydroxybutyl group, a 3-hydroxybutyl group, a 2-hydroxybutyl group, a 1-hydroxybutyl group, a 5-hydroxypentyl group, a 4-hydroxypentyl group, a 3-hydroxypentyl group, a 2-hydroxypentyl group, a 1-hydroxypentyl group, a 6-hydroxyhexyl group, a 5-hydroxyhexyl group, a 4-hydroxyhexyl group, a 3-hydroxyhexyl group, a 2-hydroxyhexyl group, a 1-hydroxyhexyl group or the like; the term "hydroxy(lower alkoxy) group" means a straight-chained or branched hydroxyalkoxy group having 2 to 6 carbon atoms such as a 2-hydroxyethoxy group, a 3-hydroxypropoxy group, a 2-hydroxypropoxy group, a 2-hydroxy-1-methylethoxy group, a 4-hydroxybutoxy group, a 3-hydroxybutoxy group, a 2-hydroxybutoxy group, a 5-hydroxypentyloxy group, a 4-hydroxypentyloxy group, a 3-hydroxypentyloxy group, a 2-hydroxypentyloxy group, a 6-hydroxyhexyloxy group, a 5-hydroxyhexyloxy group, a 4-hydroxyhexyloxy group, a 3-hydroxyhexyloxy group, a 2-hydroxyhexyloxy group or the like; and the term "hydroxy(lower alkylthio) group" means a straight-chained or branched hydroxylalkylthio group having 2 to 6 carbon atoms such as an 2-hydroxyethylthio group, a 3-hydroxypropylthio group, a 2-hydroxypropylthio group, a 2-hydroxy-1-methylethylthiogroup, a 4-hydroxybutylthiogroup, a 3-hydroxybutylthio group, a 2-hydroxybutylthio group, a 5-hydroxypentylthio group, a 4-hydroxypentylthio group, a 3-hydroxypentylthio group, a 2-hydroxypentylthio group, a 6-hydroxyhexylthio group, a 5-hydroxyhexylthio group, a 4-hydroxyhexylthio group, a 3-hydroxyhexylthio group, a 2-hydroxyhexylthio group or the like. The term "lower alkoxy-substituted (lower alkyl) group" means the above lower alkyl group substituted by the above lower alkoxy group; the term "lower alkoxy-substituted (lower alkoxy) group" means the above lower alkoxy group substituted by the above lower alkoxy group; and the term "lower alkoxy-substituted (lower alkylthio) group" means the above lower alkylthio group substituted by the above lower alkoxy group. The term "lower alkenyloxy group" a straight-chained or branched alkenyloxy group having 2 to 6 carbon atoms such as an allyloxy group; the term "hydroxy(lower alkenyl) group" means a straight-chained or branched hydroxyalkenyl group having 3 to 6 carbon atoms such as an 3-hydroxy-1-propenyl group; the term "aralkyloxy group" means the above lower alkoxy group substituted by an aryl group (e.g., a phenyl group, a naphthyl group and the like) such as a benzyloxy group; the term "aralkyloxy(lower alkyl) group" means the above lower alkyl group substituted by the above aralkyloxy group; the term "cyano(lower alkyl) group" means the above lower alkyl group substituted by a cyano group; the term "carbamoyl (lower alkyl) group" means the above lower alkyl group substituted by a carbamoyl group; and "mono ordi (lower alkyl) amino group" means an amino group mono or disubstituted by the above lower alkyl group. The term "lower alkoxy carbonyl group" means a straight-chained or branched alkoxy carbonyl group having 2 to 7 carbon atoms such as a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group, a tert-butoxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group, a neopenetyloxycarbonyl group, a tert-pentyloxycarbonyl group, a hexyloxycarbonyl group or the like; the term "lower alkoxy carbonyl-substituted (lower alkyl) group" means the above lower alkyl group substituted by the above lower alkoxy carbonyl group; the term "lower alkoxy carbonyl-substituted (lower alkoxy) group" means the above lower alkoxy group substituted by the above lower alkoxy carbonyl group; and the term "carboxy(lower alkyl) group" means the above lower alkyl group substituted by a carboxy group; and the term "carboxy (lower alkoxy) group means the above lower alkoxy group substituted by a carboxy group.

[0015] The term "hydroxy-protective group" means a hydroxy-protective group used in general organic reactions such as a benzyl group, a methoxymethyl group, an acetyl group, a benzoyl group or the like. The term "amino-protective group" means an amino-protective group used in general organic reactions such as a benzyloxycarbonyl group, a tert-butoxycarbonyl group, a phthaloyl group, a benzyl group, an acetyl group or the like.

[0016] For example, the compounds represented by the above general formula (I) of the present invention can be prepared using a benzylphenol derivative represented by the above general formula (II) of the present invention according the following procedure:



30 wherein X represents a leaving group such as a trichloroacetoimidoxy group, an acetoxy group, a bromine atom or a fluorine atom; and R¹, R², R³, R¹¹, R¹² and R¹³ have the same meanings as defined above.

Process 1

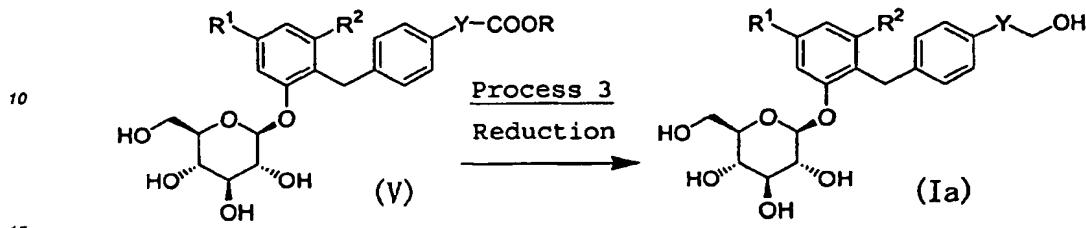
[0017] A glucoside represented by the above general formula (IV) can be prepared by subjecting a benzylphenol derivative represented by the above general formula (II) or a salt thereof to glycosidation using a glycosyl-donor represented by the above general formula (III) such as 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoxy- α -D-glucopyranose, 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoxy- β -D-glucopyranose, 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose, 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide and 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl fluoride in the presence of an activating reagent such as boron trifluoride-diethyl ether complex, silver trifluoromethanesulfonate, tin (IV) chloride or trimethylsilyl trifluoromethanesulfonate in an inert solvent. As the solvent used, dichloromethane, toluene, acetonitrile, nitromethane, ethyl acetate, diethyl ether, chloroform, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -30°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature. In addition, compounds wherein substituents R¹¹ and/or R¹³ have a hydroxy-protective group or an amino-protective group can be used in the process 2 after removing appropriately the protective group in the usual way subsequent to reaction completion of this process.

Process 2

[0018] A compound (I) of the present invention can be prepared by subjecting a glucoside represented by the above general formula (IV) to alkaline hydrolysis to remove the hydroxy-protective groups. As the solvent used, water, methanol, ethanol, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated, and as alkaline materials, sodium hydroxide, sodium methoxide, sodium ethoxide or the like can be used. The treatment temperature is usually from 0°C to reflux temperature, and the treatment time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and treatment temperature. In addition, compounds wherein substituents R¹¹ and/or R¹³ have a hydroxy-protective group or an amino-protective group can be carried out by modifying the above treatment method appropriately in the usual way and can be derived into a desired compound (I) by removing the protective group in the

usual way subsequent to reaction completion of this process.

[0019] For example, of the compounds represented by the above general formula (I) of the present invention, compounds represented by the following general formula (Ia) can be also prepared using a carboxylic acid derivative represented by the above general formula (V) according the following procedure:



wherein Y represents a straight-chained or branched alkyl group having 1 to 5 carbon atoms or a straight-chained or branched alkenyl group having 2 to 5 carbon atoms; R represents a hydrogen atom or a lower alkyl group; and R¹ and R² have the same meanings as defined above.

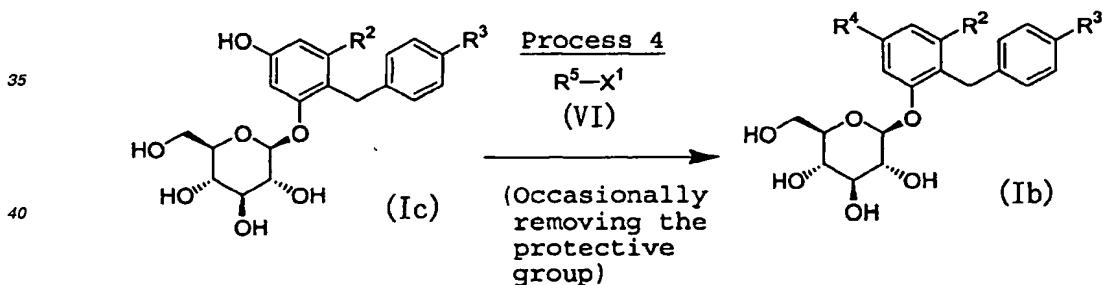
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Process 3

[0020] A compound represented by the above general formula (Ia) can be prepared by subjecting a carboxylic acid derivative represented by the above general formula (V) to reduction using a reducing agent such as lithium aluminium hydride, boran or lithiumborohydride in a solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol or a mixed solvent thereof. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

[0021] Furthermore, for example, of the compounds represented by the above general formula (I) of the present invention, compounds represented by the following general formula (Ib) can be also prepared using a phenol derivative represented by the above general formula (Ic) according the following procedure:

30



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wherein R⁴ represents a lower alkoxy group, a hydroxy(lower alkoxy)group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy carbonyl-substituted (lower alkoxy) group or a carboxy (lower alkoxy) group; R⁵ represents a lower alkyl group, a protected hydroxy(lower alkyl) group, a lower alkoxy-substituted (lower alkyl) group or a lower alkoxy-carbonyl-substituted (lower alkyl) group; X¹ represents a leaving group such as a chlorine atom, a bromine atom, an iodine atom, a mesyloxy group or tosyloxy group; and R² and R³ have the same meanings as defined above.

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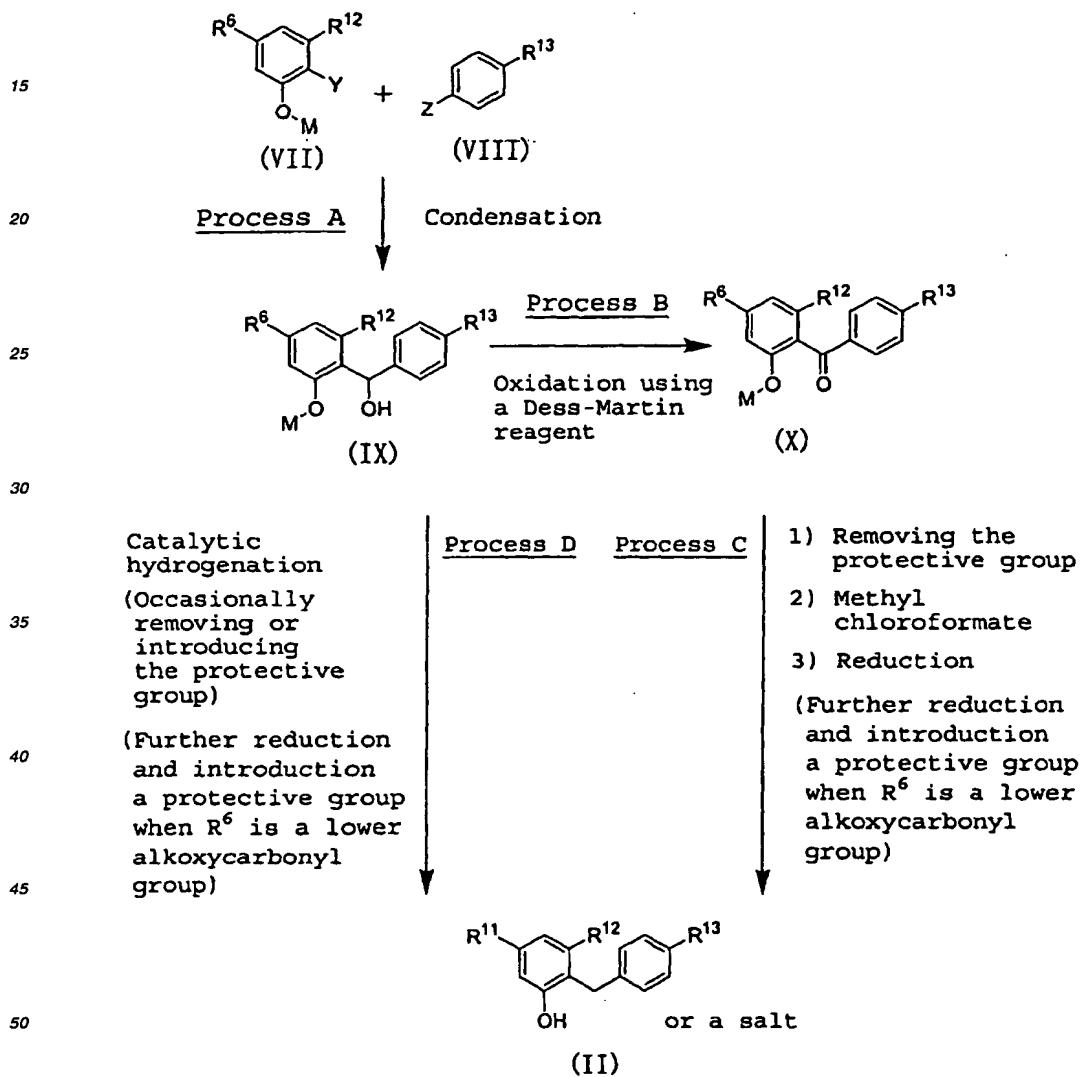
Process 4

[0022] A compound represented by the above general formula (Ib) can be prepared by subjecting a phenol derivative represented by the above general formula (Ic) to *O*-alkylation using an alkylating agent represented by the above general formula (VI) in the presence of an alkaline material such as sodium hydride, potassium carbonate, cesium carbonate, potassium *tert*-butoxide, sodium hydroxide, potassium hydroxide or sodium hydrogen carbonate in a solvent such as tetrahydrofuran, *N,N*-dimethylformamide, dimethyl sulfoxide, acetonitrile or a mixed solvent thereof, and removing the protective group in the usual way as occasion demands. The reaction temperature is usually from 0°C to

reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

[0023] Of the compounds represented by the above general formula (IV), compounds wherein R¹¹ represents a protected mono(lower alkyl)amino group can be prepared by allowing a corresponding compound wherein R¹¹ represents a protected amino group to react with an appropriate alkylating agent such as a lower alkyl halide, a mesylate compound or a tosylate compound in the presence of an alkaline material such as sodium hydride or potassium carbonate in a solvent such as tetrahydrofuran, N,N-dimethylformamide, dimethyl sulfoxide or a mixed solvent thereof.

[0024] For example, the compounds represented by the above general formula (II) of the present invention which are used as starting materials in the aforementioned production process and salts thereof can be prepared according to the following procedure:



wherein M represents hydrogen atom or a hydroxy-protective group; R⁶ represents a hydrogen atom, a protected hydroxy group, a protected amino group, a protected mono (lower alkyl) amino group, a di(lower alkyl)amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a protected hydroxy(lower alkyl) group, a protected hydroxy (lower alkoxy) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-sub-

stituted (lower alkoxy) group, a carboxy(lower alkyl) group, a carboxy(lower alkoxy) group or a lower alkoxy carbonyl group; one of Y and Z represents MgBr, MgCl, MgI or a lithium atom, while the other represents a formyl group; and R, R¹² and R¹³ have the same meanings as defined above.

5 Process A

[0025] A compound represented by the above general formula (IX) can be prepared by condensing a benzaldehyde derivative represented by the above general formula (VII) with a Grignard reagent or a lithium reagent represented by the above general formula (VIII), or by condensing a Grignard reagent or a lithium reagent represented by the above general formula (VII) with a benzaldehyde derivative represented by the above general formula (VIII) in an inert solvent. As the solvent used, tetrahydrofuran, diethyl ether, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from -78°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

10 Process B

[0026] A compound represented by the above general formula (X) can be prepared by subjecting a compound represented by the above general formula (IX) to oxidation using a Dess-Martin reagent in an inert solvent. As the solvent used, dichloromethane, chloroform, acetonitrile, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature.

15 Process C

[0027] A compound represented by the above general formula (II) of the present invention can be prepared by removing the protective group of a compound represented by the above general formula (X) in the usual way, condensing the resulting compound with methyl chloroformate in the presence of a base such as triethylamine, diisopropylethylamine or 4-(N,N-dimethylamino) pyridine in an inert solvent and subjecting the resulting carbonate compound to reduction using a reducing agent such as sodium borohydride. As the solvent used in the condensing reaction, tetrahydrofuran, dichloromethane, acetonitrile, ethyl acetate, diethyl ether, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature. As the solvent used in the reducing reaction, a mixed solvent with tetrahydrofuran and water, and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature. In the case where R⁶ represents a lower alkoxy carbonyl group, the corresponding compounds can be derived into the compound represented by the above general formula (II) of the present invention by reducing said group using a reducing agent such as lithium aluminium hydride in an inert solvent into a hydroxymethyl group and protecting the hydroxy group in the usual way. As the solvent used in the reducing reaction, diethyl ether, tetrahydrofuran, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on starting material used, solvent and reaction temperature. In addition, the compounds represented by the above general formula (II) of the present invention can be converted into a salt thereof such as a sodium salt or a potassium salt in the usual way.

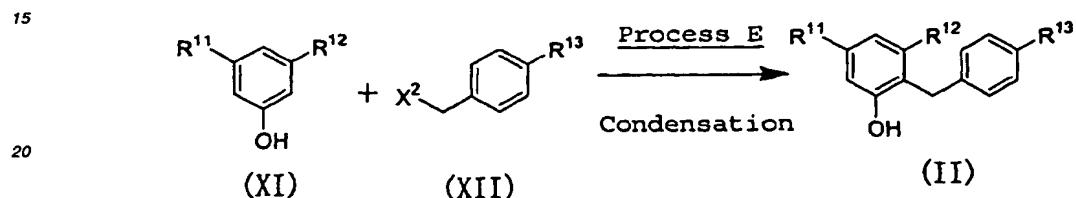
20 Process D

[0028] A compound represented by the above general formula (II) of the present invention can be prepared by subjecting a compound represented by the above general formula (IX) to catalytic hydrogenation using a palladium catalyst such as palladium-carbon in the presence or absence of an acid such as hydrochloric acid in an inert solvent, and removing or introducing the protective group in the usual way as occasion demands. As the solvent used in the catalytic hydrogenation, methanol, ethanol, tetrahydrofuran, ethyl acetate, acetic acid, isopropanol, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature. In the case where R⁶ represents a lower alkoxy carbonyl group, the corresponding compounds can be converted into the compound represented by the above general formula (II) of the present invention by reducing said group using a reducing agent such as lithium aluminium hydride in an inert solvent into a hydroxymethyl group and protecting the hydroxy group in the usual way. As the solvent used in the reducing reaction, diethyl ether, tetrahydrofuran, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and

the reaction time is usually from 10 minutes to 1 day, varying based on starting material used, solvent and reaction temperature. In addition, the compound of the above general formula (II) of the present invention can be converted into a salt thereof such as a sodium salt or a potassium salt in the usual way.

[0029] In the compounds represented by the above general formulae (II), (VII), (VIII), (IX) and (X), compounds where-in substituents R¹¹ and/or R¹³ represent a carboxy group, an amino group, a cyano group, a carbamoyl group, a hydroxy (lower alkyl) group, a carboxy(lower alkyl) group, a carboxy(lower alkenyl) group, a lower alkoxy carbonyl-substituted (lower alkyl) group, a lower alkoxy carbonyl-substituted (lower alkenyl) group, an amino(lower alkyl) group, a cyano (lower alkyl) group, a carbamoyl(lower alkyl) group or the like can be prepared by converting appropriately from the corresponding compound having a lower alkoxy carbonyl group as a substituent in the usual way and can be used in the subsequent processes (processes A-D and 1).

[0030] The compounds represented by the above general formula (II) of the present invention which are used as starting materials in the aforementioned production process and salts thereof can be also prepared according the following procedure:



25 wherein X² represents a leaving group such as a chlorine atom; and R¹¹, R¹² and R¹³ have the same meanings as defined above.

Process E

[0031] A compound represented by the above general formula (II) can be prepared by subjecting a phenol derivative represented by the above general formula (XI) to benzylation using a benzyl derivative represented by the above general formula (XII) in the presence of an alkaline material such as lithium hydroxide without any solvent. The reaction temperature is usually from 50 to 200°C, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

[0032] The compounds of the present invention obtained by the above production processes can be isolated and purified by conventional separation means such as fractional recrystallization, purification using chromatography, solvent extraction and solid phase extraction.

[0033] The glucopyranosyloxybenzylbenzene derivatives represented by the above general formula (I) of the present invention can be converted into their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts with mineral acids (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like), acid addition salts with organic acids (e.g., acetic acid, adipic acid, citric acid, fumaric acid, maleic acid, oleic acid, lactic acid, stearic acid, succinic acid, tartaric acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid and the like), salts with organic amines (e.g., 2-aminoethanol, piperidine, morpholine, pyrrolidine and the like), and salts with an inorganic base such as a sodium salt, a potassium salt, a calcium salt or a magnesium salt.

[0034] The compounds represented by the above general formula (I) of the present invention include their hydrates and their solvates with pharmaceutically acceptable solvents such as ethanol.

[0035] Of the compounds represented by the above general formula (I) of the present invention, compounds having an unsaturated bond exist in two geometrical isomer forms. Either cis(Z)-isomer or trans(E)-isomer can be employed in the present invention.

[0036] Of the compounds represented by the above general formula (I) of the present invention, compounds having an asymmetric carbon atom with the exception of the glucopyranosyloxy moiety exist in two optical isomer forms of (*R*) configuration and (*S*) configuration. Either one of the isomers or a mixture thereof can be employed in the present invention.

[0037] The compounds represented by the above general formula (I) and the pharmaceutically acceptable salts thereof of the present invention have an excellent inhibitory activity in human SGLT2 and are extremely useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complication or obesity. In the following assay for inhibitory effect on human SGLT2 activity, compounds of the present invention exerted a potent inhibitory activity in human SGLT2.

[0038] When the pharmaceutical compositions of the present invention are employed in practical treatment, various

dosage forms are used depending on their uses . As examples of the dosage forms, powders, granules, fine granules, dry syrups, tablets, capsules, injections, solutions, ointments, suppositories, poultices and the like are illustrations, which are orally or parenterally administered.

5 [0039] These pharmaceutical compositions can be prepared by admixing with or by diluting and dissolving an appropriate pharmaceutical additive such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents, dissolving aids and the like, and formulating the mixture in accordance with conventional practice.

10 [0040] When the pharmaceutical compositions of the present invention are employed in practical treatment, the dosage of a compound represented by the above general formula (I) or a pharmaceutically acceptable salt thereof of the present invention as the active ingredient is appropriately decided depending on the age, sex, body weight and degree of symptoms and treatment of each patient, which is approximately within the range of from 0.1 to 1,000mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 300mg per day per adult human in the case of parenteral administration, and the daily dose can be divided into one to several doses per day and administered suitably.

15

Example

20 [0041] The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. However, the present invention is not limited thereto.

25

Reference Example 1

Methyl 4-[(2-benzyloxyphenyl)hydroxymethyl]benzoate

30 [0042] A Grignard reagent was prepared from 1-benzyloxy-2-bromobenzene (5.3g), magnesium (0.49g) and tetrahydrofuran (160mL). The obtained Grignard reagent was added to a solution of methyl 4-formylbenzoate (3.3g) in tetrahydrofuran (60mL), and the mixture was stirred at room temperature for 1 hour. To the reaction mixture were added water and dilute hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure.

35 The residue was purified by column chromatography on aminopropyl silica gel (eluent: hexane/ethyl acetate = 4/1) to give methyl 4-[(2-benzyloxyphenyl)hydroxymethyl]benzoate (2.6g).

¹H-NMR (CDCl₃) δ ppm:

3.02 (1H, d, J=6.3Hz), 3.91 (3H, s), 5.00 (1H, d, J=11.6Hz), 5.04 (1H, d, J=11.6Hz), 6.07 (1H, d, J=6.3Hz), 6.90-7.05 (2H, m), 7.15-7.35 (7H, m), 7.35-7.45 (2H, m), 7.90-8.00 (2H, m)

40

Example 1

Methyl 4-(2-hydroxybenzyl)benzoate

45 [0043] To a solution of methyl 4-[(2-benzyloxyphenyl)-hydroxymethyl]benzoate (2.6g) in ethanol (15mL) was added 10% palladium-carbon powder (0.50g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 18 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure to give methyl 4-(2-hydroxybenzyl)benzoate (1.7g).

¹H-NMR (CDCl₃) δ ppm:

3.89 (3H, s), 4.04 (2H, s), 4.80 (1H, s), 6.75-6.80 (1H, m), 6.85-6.95 (1H, m), 7.05-7.20 (2H, m), 7.25-7.35 (2H, m), 7.90-8.00 (2H, m)

Reference Example 2

Methyl 4-(2-benzyloxybenzyl)benzoate

50 [0044] To a suspension of methyl 4-(2-hydroxybenzyl)benzoate (1.5g) and potassium carbonate (0.94g) in N,N-dimethylformamide (200mL) was added benzylbromide (0.81mL), and the mixture was stirred at 50°C for 5 hours. An insoluble material was removed by filtration, water and dilute hydrochloric acid was added to the filtrate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give methyl 4-(2-benzyloxybenzyl)benzoate (2.1g).

¹H-NMR (CDCl₃) δ ppm:

3.89 (3H, s), 4.06 (2H, s), 5.03 (2H, s), 6.85-6.95 (2H, m), 7.10-7.40 (9H, m), 7.85-7.95 (2H, m)

Reference Example 3

5 4-(2-Benzylbenzyl)benzyl alcohol

[0045] To a suspension of lithium aluminum hydride (0.47g) in tetrahydrofuran (5mL) was added dropwise a solution of methyl 4-(2-benzylbenzyl)benzoate (2.1g) in tetrahydrofuran (5mL) at 0°C, and the mixture was stirred at the same temperature for 1 hour. Ethyl acetate (10mL) was added to the reaction mixture, and the resulting mixture was stirred for 30 minutes. To the reaction mixture were added water and dilute hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 4-(2-benzylbenzyl)benzyl alcohol (1.9g).

¹H-NMR (CDCl₃) δ ppm:

4.02 (2H, s), 4.65 (2H, s), 5.06 (2H, s), 6.85-6.95 (2H, m), 7.05-7.40. (11H, m)

15

Reference Example 4

4-(2-Benzylbenzyl)benzaldehyde

20 [0046] To a solution of 4-(2-benzylbenzyl)benzyl alcohol (1.0g) in dichloromethane (50mL) was added manganese (II) oxide (10g), and the mixture was stirred at room temperature for 3 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure to give 4-(2-benzylbenzyl)benzaldehyde (0.97g).

¹H-NMR (CDCl₃) δ ppm:

25 4.08 (2H, s), 5.03 (2H, s), 6.90-7.00 (2H, m), 7.10-7.40 (9H, m), 7.70-7.80 (2H, m), 9.96 (1H, s)

Reference Example 5

Ethyl (E)-3-[4-(2-hydroxybenzyl)phenyl]acrylate

30

[0047] To a solution of triethyl phosphonoacetate (0.89mL) in tetrahydrofuran (30mL) was added potassium tert-butoxide (0.50g), and the mixture was stirred at room temperature for 15 minutes. A solution of 4-(2-benzylbenzyl)benzaldehyde (1.0g) in tetrahydrofuran (10mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 6 hours. To the reaction mixture was added dilute hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10/1) to give ethyl (E)-3-[4-(2-benzylbenzyl)phenyl]acrylate (0.86g). To the obtained ethyl (E)-3-[4-(2-benzylbenzyl)phenyl]acrylate (0.86g) were added trifluoroacetic acid (9.5mL), water (0.5mL) and dimethyl sulfide (1.0mL), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) to give ethyl (E)-3-[4-(2-hydroxybenzyl)phenyl]acrylate (0.51g).

¹H-NMR (CDCl₃) δ ppm:

1.33 (3H, t, J=7.2Hz), 4.01 (2H, s), 4.26 (2H, q, J=7.2Hz), 4.96 (1H, s), 6.38 (1H, d, J=16.1Hz), 6.75-6.80 (1H, m), 6.85-6.95 (1H, m), 7.05-7.20 (2H, m), 7.20-7.30 (2H, m), 7.40-7.50 (2H, m), 7.65 (1H, d, J=16.1Hz)

45

Reference Example 6

(E)-2-[4-(2-Ethoxycarbonylvinyl)benzyl]phenyl β-D-glucopyranoside

50 [0048] To a suspension of ethyl (E)-3-[4-(2-hydroxybenzyl)phenyl]acrylate (0.34g) and 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (1.4g) in dichloromethane (3mL) and toluene (9mL) was added boron trifluoride-diethyl ether complex (0.45mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=4/1) to give (E)-2-[4-(2-ethoxycarbonylvinyl)benzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.47g). To a solution of the obtained (E)-2-[4-(2-ethoxycarbonylvinyl)benzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.46g) in methanol (5mL) was added sodium methoxide (0.010g), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give (E)-2-[4-(2-ethoxycarbonylvinyl)benzyl]

phenyl β -D-glucopyranoside (0.31g).

$^1\text{H-NMR}$ (CD_3OD) δ ppm:
 1.31 (3H, t, $J=7.2\text{Hz}$), 3.30-3.55 (4H, m), 3.68 (1H, dd, $J=5.3, 12.0\text{Hz}$), 3.88 (1H, dd, $J=1.9, 12.0\text{Hz}$), 4.00 (1H, d, $J=14.9\text{Hz}$), 4.15 (1H, dd, $J=14.9\text{Hz}$), 4.22 (2H, q, $J=7.2\text{Hz}$), 4.92 (1H, d, $J=7.1\text{Hz}$), 6.45 (1H, d, $J=16.1\text{Hz}$), 6.90-7.00 (1H, m), 7.05-7.20 (3H, m), 7.25-7.35 (2H, m), 7.45-7.55 (2H, m), 7.64 (1H, d, $J=16.1\text{Hz}$)

5 Reference Example 7

2-(4-Methoxycarbonylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

10 [0049] To a suspension of methyl 4-(2-hydroxybenzyl)benzoate (0.053g) and 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose (0.26g) in dichloromethane (1mL) and toluene (3mL) was added boron trifluoride-diethyl ether complex (0.083mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 2-(4-methoxycarbonylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.067g).

15 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
 1.87 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.80-4.05 (6H, m), 4.16 (1H, dd, $J=2.7, 12.4\text{Hz}$), 4.28 (1H, dd, $J=5.8, 12.4\text{Hz}$), 5.10-5.20 (2H, m), 5.25-5.35 (2H, m), 6.95-7.10 (3H, m), 7.15-7.25 (3H, m), 7.90-7.95 (2H, m)

20 Reference Example 8

4-Allyloxy-2'-(methoxymethoxy)diphenylmethanol

25 [0050] A Grignard reagent was prepared from 1-allyloxy-4-bromobenzene (1.7g), magnesium (0.19g), a catalytic amount of iodine and tetrahydrofuran (3mL). To the obtained Grignard reagent was added a solution of 2-(methoxymethoxy)-benzaldehyde (0.88g) in tetrahydrofuran (19mL), and the mixture was stirred at room temperature for 30 minutes. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate =5/1) to give 4-allyloxy-2'-(methoxymethoxy)diphenylmethanol (1.2g).

30 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
 2.78 (1H, d, $J=5.4\text{Hz}$), 3.31 (3H, s), 4.45-4.55 (2H, m), 5.12 (1H, d, $J=7.0\text{Hz}$), 5.14 (1H, d, $J=7.0\text{Hz}$), 5.20-5.30 (1H, m), 5.35-5.45 (1H, m), 5.95-6.10 (2H, m), 6.80-6.90 (2H, m), 6.95-7.05 (1H, m), 7.07 (1H, dd, $J=0.9, 8.2\text{Hz}$), 7.20-7.35 (3H, m), 7.35 (1H, dd, $J=1.8, 7.7\text{Hz}$)

35 Reference Example 9

4-Allyloxy-2'-(methoxymethoxy)benzophenone

40 [0051] To a solution of 4-allyloxy-2'-(methoxymethoxy)-diphenylmethanol (1.2g) in dichloromethane (20mL) was added a Dess-Martin reagent (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3- (1*H*) -one) (2.1g) at 0°C, and the mixture was stirred for 1 hour. The reaction mixture was warmed to ambient temperature and stirred overnight. Diethyl ether and 1 mol/L aqueous sodium hydroxide solution were added to the reaction mixture, and the organic layer was separated. The organic layer was washed with 1 mol/L aqueous sodium hydroxide solution, water and brine, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 4-allyloxy-2'-(methoxymethoxy)benzophenone (1.1g).

45 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
 3.33 (3H, s), 4.55-4.65 (2H, m), 5.08 (2H, s), 5.25-5.35 (1H, m), 5.35-5.50 (1H, m), 6.00-6.15 (1H, m), 6.85-7.00 (2H, m), 7.05-7.15 (1H, m), 7.15-7.25 (1H, m), 7.33 (1H, dd, $J=1.5, 7.7\text{Hz}$), 7.35-7.50 (1H, m), 7.75-7.85 (2H, m)

50 Reference Example 10

4-Allyloxy-2'-hydroxybenzophenone

55 [0052] To a solution of 4-allyloxy-2'-(methoxymethoxy)-benzophenone (1.1g) in ethanol (15mL) was added concentrated hydrochloric acid (0.96mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and a saturated aqueous sodium hydrogen carbonate solution was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over

anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15/1) to give 4-allyloxy-2'-hydroxybenzophenone (0.87g).
¹H-NMR (CDCl_3) δ ppm:

5 4.60-4.70 (2H, m), 5.30-5.40 (1H, m), 5.40-5.50 (1H, m), 6.00-6.15 (1H, m), 6.85-6.95 (1H, m), 6.95-7.05 (2H, m), 7.07 (1H, dd, J=1.0, 8.4Hz), 7.45-7.55 (1H, m), 7.63 (1H, dd, J=1.6, 8.0Hz), 7.65-7.75 (2H, m), 11.96(1H, s)

Example 2

2-(4-Allyloxybenzyl)phenol

10 [0053] To a solution of 4-allyloxy-2'-hydroxybenzophenone (0.87g) in tetrahydrofuran (14mL) were added triethylamine (0.53mL) and methyl chloroformate (0.29mL) at 0°C, and the mixture was stirred at room temperature for 1.5 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. To a solution of the residue in tetrahydrofuran (18mL) and water (9mL) was added sodium borohydride (0.52g) at 0°C, and the mixture was stirred at room temperature for 2.5 hours. To the reaction mixture was added 0.5 mol/L aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 8/1) to give 2-(4-allyloxybenzyl)phenol (0.72g).

15 20 ¹H-NMR (CDCl_3) δ ppm:
3.93 (2H, s), 4.45-4.55 (2H, m), 4.73 (1H, brs), 5.20-5.30 (1H, m), 5.35-5.45 (1H, m), 5.95-6.10 (1H, m), 6.78 (1H, dd, J=1.3, 7.9Hz), 6.80-6.95 (3H, m), 7.05-7.20 (4H, m)

Reference Example 11

2-(4-Allyloxybenzyl) phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

25 [0054] To a solution of 2-(4-allyloxybenzyl)phenol (0.20g) and 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoxy- α -D-glucopyranose (0.45g) in dichloromethane (8.5mL) was added boron trifluoride-diethyl ether complex (0.12g), and the mixture was stirred at room temperature for 2 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1) to give 2-(4-allyloxybenzyl) phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.44g).

30 35 ¹H-NMR (CDCl_3) δ ppm:
1.90 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.80-3.95 (3H, m), 4.18 (1H, dd, J=2.5, 12.3Hz), 4.28 (1H, dd, J=5.5, 12.3Hz), 4.45-4.55 (2H, m), 5.11 (1H, d, J=7.5Hz), 5.10-5.45 (5H, m), 5.95-6.10 (1H, m), 6.75-6.85 (2H, m), 6.95-7.10 (5H, m), 7.10-7.20 (1H, m)

40 Reference Example 12

4-(2-Benzylxyethyl)-2'-(methoxymethoxy)diphenylmethanol

45 [0055] The title compound was prepared in a similar manner to that described in Reference Example 8 using 4-(2-benzylxyethyl)-1-bromobenzene instead of 4-allyloxy-1-bromobenzene.

¹H-NMR (CDCl_3) δ ppm:
2.80 (1H, d, J=5.7Hz), 2.90 (2H, t, J=7.1Hz), 3.30 (3H, s), 3.66 (2H, t, J=7.1Hz), 4.51 (2H, s), 5.10-5.20 (2H, m), 6.06 (1H, d, J=5.7Hz), 6.95-7.05 (1H, m), 7.05-7.10 (1H, m), 7.10-7.20 (2H, m), 7.20-7.40 (9H, m)

50 Reference Example 13

4-(2-Benzylxyethyl)-2'-(methoxymethoxy)benzophenone

55 [0056] The title compound was prepared in a similar manner to that described in Reference Example 9 using 4-(2-benzylxyethyl)-2'-(methoxymethoxy)diphenylmethanol instead of 4-allyloxy-2'-(methoxymethoxy)diphenylmethanol.

¹H-NMR (CDCl_3) δ ppm:
2.98 (2H, t, J=6.8Hz), 3.29 (3H, s), 3.72 (2H, t, J=6.8Hz), 4.51 (2H, s), 5.05 (2H, s), 7.05-7.15 (1H, m), 7.15-7.25 (1H, m), 7.25-7.40 (8H, m), 7.40-7.50 (1H, m), 7.70-7.80 (2H, m)

Reference Example 14

4- (2-Benzylxyethyl) -2' -hydroxybenzophenone

5 [0057] The title compound was prepared in a similar manner to that described in Reference Example 10 using 4-(2-benzylxyethyl)-2'-(methoxymethoxy)benzophenone instead of 4-allyloxy-2' - (methoxymethoxy) benzophenone.

10 ¹H-NMR (CDCl₃) δ ppm:
3.02 (2H, t, J=6.8Hz), 3.75 (2H, t, J=6.8Hz), 4.55 (2H, s), 6.85-6.90 (1H, m), 7.05-7.10 (1H, m), 7.25-7.40 (7H, m),
7.45-7.55 (1H, m), 7.55-7.65 (3H, m), 12.02 (1H, s)

Example 3

2-[4-(2-Benzylxyethyl)benzyl]phenol

15 [0058] The title compound was prepared in a similar manner to that described in Example 2 using 4-(2-benzylxyethyl)-2'-hydroxybenzophenone instead of 4-allyloxy-2'-hydroxybenzophenone.

1H-NMR (CDCl₃) δ ppm:
2.90 (2H, t, J=7.2Hz), 3.66 (2H, t, J=7.2Hz), 3.97 (2H, s), 4.52 (2H, s), 4.62 (1H, s), 6.75-6.85 (1H, m), 6.85-6.95 (1H, m),
7.05-7.20 (6H, m), 7.20-7.40 (5H, m)

Reference Example 15

4- (2-Benzylxyethyl)benzyl chloride

25 [0059] To a solution of 4-(2-benzylxyethyl)benzyl alcohol (0.67g) in dichloromethane (30mL) was added thionyl chloride (0.48mL), and the mixture was heated under reflux for 1 hour. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give 4-(2-benzylxyethyl)benzyl chloride (0.68g).

30 ¹H-NMR (CDCl₃) δ ppm:
4.01 (2H, s), 4.56 (2H, s), 5.04 (2H, s), 6.85-7.40 (13H, m)

Reference Example 16

[4-(2-Benzylxyethyl)phenyl]acetonitrile

35 [0060] To a solution of 4-(2-benzylxyethyl)benzyl chloride (0.66g) in N,N-dimethylformamide (20mL) was added potassium cyanide (0.40g), and the mixture was stirred at 60°C for 18 hours. The reaction mixture was cooled to ambient temperature, and water was added thereto. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1-3/1) to give [4-(2-benzylxyethyl) phenyl] acetonitrile (0.54g).

40 ¹H-NMR (CDCl₃) δ ppm:
3.70 (2H, s), 4.01 (2H, s), 5.04 (2H, s), 6.85-7.40 (13H, m)

Example 4

[4-(2-Hydroxybenzyl)phenyl]acetonitrile

50 [0061] Trifluoroacetic acid (17mL), water (1mL) and dimethyl sulfide (2mL) were added to [4-(2-benzylxyethyl) phenyl]-acetonitrile (0.41g), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate =3/1) to give [4-(2-hydroxybenzyl)phenyl]acetonitrile (0.26g).

55 ¹H-NMR (CDCl₃) δ ppm:
3.71 (2H, s), 3.99 (2H, s), 4.76 (1H, s), 6.77 (1H, dd, J=1.1, 7.9Hz), 6.89 (1H, dt, 1.1, 7.5Hz), 7.05-7.20 (2H, m),
7.20-7.30 (4H, m)

Reference Example 17

4-(2-Benzylbenzyl)benzoic acid

5 [0062] To a solution of methyl 4-(2-benzylbenzyl)benzoate (1.0g) in methanol (20mL) was added 2 mol/L aqueous sodium hydroxide solution (7.5mL), and the mixture was stirred at 60°C for 5 hours. The reaction mixture was concentrated under reduced pressure. After the residue was acidified by adding dilute hydrochloric acid, the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 4-(2-benzylbenzyl)benzoic acid (0.72g).

10 ¹H-NMR (DMSO-d₆) δ ppm:

4.01 (2H, s), 5.09 (2H, s), 6.85-6.95 (1H, m), 7.00-7.10 (1H, m), 7.15-7.40 (9H, m), 7.75-7.85 (2H, m), 12.77 (1H, brs)

Reference Example 18

4-(2-Benzylbenzyl)benzamide

15 [0063] To a suspension of 4-(2-benzylbenzyl)benzoic acid (0.70g) in dichloromethane (10mL) was added thionyl chloride (0.48mL), and the mixture was stirred at 50°C for 3 hours. The reaction mixture was concentrated under reduced pressure, and 28% aqueous ammonium solution (50mL) was added to the residue. The mixture was stirred at room temperature for 30 minutes. An insoluble material was collected by filtration, washed with water then hexane, and dried under reduced pressure to give 4-(2-benzylbenzyl)benzamide (0.62g).

20 ¹H-NMR (DMSO-d₆) δ ppm:

3.98 (2H, s), 5.10 (2H, s), 6.85-6.95 (1H, m), 7.00-7.10 (1H, m), 7.15-7.40 (10H, m), 7.70-7.80 (2H, m), 7.88 (1H, brs)

Example 5

4-(2-Hydroxybenzyl)benzamide

25 [0064] To a solution of 4-(2-benzylbenzyl)benzamide (0.50g) in ethanol (10mL) was added 10% palladium-carbon powder (0.10g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hour. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure to give 4-(2-hydroxybenzyl)benzamide (0.31g).

30 ¹H-NMR (DMSO-d₆) δ ppm:

3.90 (2H, s), 6.65-6.75 (1H, m), 6.75-6.85 (1H, m), 6.95-7.10 (2H, m), 7.20-7.30 (3H, m), 7.70-7.80 (2H, m), 7.86 (1H, brs), 9.40 (1H, s)

Reference Example 19

2-Benzyl-4'-(N,N-dimethylamino)diphenylmethanol

35 [0065] The title compound was prepared in a similar manner to that described in Reference Example 8 using 2-benzylbenzyl-1-bromobenzene and 4-(N,N-dimethylamino)benzaldehyde instead of 4-allyloxy-1-bromobenzene and 2-(methoxymethoxy)-benzaldehyde.

¹H-NMR (CDCl₃) δ ppm:

40 2.77 (1H, d, J=5.3Hz), 2.93 (6H, s), 5.04 (2H, s), 6.03 (1H, d, J=5.3Hz), 6.65-6.75 (2H, m), 6.85-7.05 (2H, m), 7.15-7.45 (9H, m)

Example 6

2-[4-(N,N-Dimethylamino)benzyl]phenol

45 [0066] To a solution of 2-benzyl-4'-(N,N-dimethylamino)diphenylmethanol (0.85g) in ethanol (25mL) was added 10% palladium-carbon powder (0.34g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 22 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 2-[4-(N,N-dimethylamino)benzyl]phenol (0.35g).

50 ¹H-NMR (CDCl₃) δ ppm:

2.91 (6H, s), 3.91 (2H, s), 4.73 (1H, s), 6.65-6.75 (2H, m), 6.75-6.85 (1H, m), 6.85-6.95 (1H, m), 7.05-7.20 (4H, m)

Reference Example 20

2-[4-(*N,N*-Dimethylamino)benzyl]phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

5 [0067] The title compound was prepared in a similar manner to that described in Reference Example 11 using 2-[4-(*N,N*-dimethylamino)benzyl]phenol instead of 2-(4-allyloxybenzyl)phenol.

1H-NMR ($CDCl_3$) δ ppm:
 1.92 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 2.89 (6H, s), 3.80-3.90 (3H, m), 4.18 (1H, dd, $J=2.3, 12.2$ Hz),
 4.28 (1H, dd, $J=5.7, 12.2$ Hz), 5.09 (1H, d, $J=7.7$ Hz), 5.15-5.25 (1H, m), 5.25-5.40 (2H, m), 6.60-6.70 (2H, m), 6.90-7.10
 10 (5H, m), 7.10-7.20 (1H, m)

Reference Example 21

4-Benzylxy-2'-(methoxymethoxy)diphenylmethanol

15 [0068] The title compound was prepared in a similar manner to that described in Reference Example 8 using 1-bromo-2-(methoxymethoxy)benzene and 4-benzylxybenzaldehyde instead of 1-allyloxy-4-bromobenzene and 2-(methoxymethoxy)-benzaldehyde.

1H-NMR ($CDCl_3$) δ ppm:
 20 2.78 (1H, d, $J=5.4$ Hz), 3.29 (3H, s), 5.04 (2H, s), 5.10-5.20 (2H, m), 6.03 (1H, d, $J=5.4$ Hz), 6.85-6.95 (2H, m), 6.95-7.10
 (2H, m), 7.20-7.45 (9H, m)

Reference Example 22

4-Benzylxy-2'-(methoxymethoxy)benzophenone

25 [0069] The title compound was prepared in a similar manner to that described in Reference Example 9 using 4-benzylxy-2'-(methoxymethoxy)diphenylmethanol instead of 4-allyloxy-2'-(methoxymethoxy)diphenylmethanol.

1H-NMR ($CDCl_3$) δ ppm:
 30 3.31 (3H, s), 5.07 (2H, s), 5.13 (2H, s), 6.95-7.05 (2H, m), 7.05-7.15 (1H, m), 7.15-7.25 (1H, m), 7.30-7.50 (7H, m),
 7.75-7.85 (2H, m)

Reference Example 23

4-Benzylxy-2'-hydroxybenzophenone

35 [0070] The title compound was prepared in a similar manner to that described in Reference Example 10 using 4-benzylxy-2'-(methoxymethoxy)benzophenone instead of 4-allyloxy-2'-(methoxymethoxy)benzophenone.

1H-NMR ($CDCl_3$) δ ppm:
 40 5.16 (2H, s), 6.85-6.95 (1H, m), 7.00-7.10 (3H, m), 7.30-7.55 (6H, m), 7.63 (1H, dd, $J=1.9, 8.2$ Hz), 7.65-7.75 (2H, m),
 11.95 (1H, s)

Example 7

2-[(4-Benzylxy)benzyl]phenol

45 [0071] The title compound was prepared in a similar manner to that described in Example 2 using 4-benzylxy-2'-hydroxybenzophenone instead of 4-allyloxy-2'-hydroxybenzophenone.

1H-NMR ($CDCl_3$) δ ppm:
 50 3.94 (2H, s), 4.70 (1H, s), 5.03 (2H, s), 6.75-6.80 (1H, m), 6.85-6.95 (3H, m), 7.05-7.20 (4H, m), 7.25-7.45 (5H, m)

Reference Example 24

2-[(4-Benzylxy)benzyl]phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

55 [0072] The title compound was prepared in a similar manner to that described in Reference Example 11 using 2-[4-(benzylxy)benzyl]phenol instead of 2-(4-allyloxybenzyl)phenol.

1H-NMR ($CDCl_3$) δ ppm:

1.88 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 3.80-3.90 (3H, m), 4.17 (1H, dd, J=2.4, 12.3Hz), 4.28 (1H, dd, J=5.7, 12.3Hz), 5.03 (2H, s), 5.10 (1H, d, J=7.2Hz), 5.15-5.25 (1H, m), 5.25-5.40 (2H, m), 6.85-6.90 (2H, m), 6.95-7.10 (5H, m), 7.10-7.20 (1H, m), 7.25-7.45 (5H, m)

5 Reference Example 25

1-Bromo-4-[2-(methoxymethoxy)ethyl]benzene

[0073] To a solution of 2-(4-bromophenyl)ethanol (1.0g and diisopropylethylamine (1.3mL) in dichloromethane (5mL) was added chloromethyl methyl ether (0.75mL), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added water, and the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 15/1-10/1) to give 1-bromo-4-[2-(methoxymethoxy)ethyl]-benzene (1.2g).

15 ¹H-NMR (CDCl_3) δ ppm: 2.85 (2H, t, J=6.8Hz), 3.28 (3H, s), 3.74 (2H, t, J=6.8Hz), 4.60 (2H, s), 7.05-7.15 (2H, m), 7.35-7.45 (2H, m)

Reference Example 26

20 2-Hydroxy-4-methoxy-4'-[2-(methoxymethoxy)ethyl]diphenylmethanol

[0074] To a solution of 1-bromo-4-[2-(methoxymethoxy)-ethyl]benzene (0.61g) in tetrahydrofuran (12mL) was added tert-butyl lithium (1.5 mol/L pentane solution, 1.8mL) under an argon atmosphere at -78°C, and the mixture was stirred for 30 minutes. A solution of 2-hydroxy-4-methoxybenzaldehyde (0.15g) in tetrahydrofuran (6mL) was added to the reaction mixture, and the mixture was warmed to 0°C and stirred for 25 minutes. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 2/1) to give 2-hydroxy-4-methoxy-4'-[2-(methoxymethoxy)ethyl]diphenylmethanol (0.31g).

15 ¹H-NMR (CDCl_3) δ ppm: 2.77 (1H, d, J=2.9Hz), 2.90 (2H, t, J=6.9Hz), 3.29 (3H, s); 3.70-3.80 (5H, m), 4.61 (2H, s), 5.96 (1H, d, J=2.9Hz), 6.35 (1H, dd, J=2.1, 8.5Hz), 6.48 (1H, d, J=2.1Hz), 6.70 (1H, d, J=8.5Hz), 7.20-7.35 (4H, m), 8.04 (1H, s)

Example 8

35 5-Methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenol

[0075] To a solution of 2-hydroxy-4-methoxy-4'-[2-(methoxymethoxy)ethyl]diphenylmethanol (0.31g) methanol (10mL) was added 10% palladium-carbon powder (0.061g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hour. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/2) to give 5-methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenol (0.19g).

40 ¹H-NMR (CDCl_3) δ ppm: 2.86 (2H, t, J=7.0Hz), 3.29 (3H, s), 3.74 (2H, t, J=7.0Hz), 3.76 (3H, s), 3.90 (2H, s), 4.61 (2H, s), 4.77 (1H, s), 6.38 (1H, d, J=2.5Hz), 6.45 (1H, dd, J=2.5, 8.5Hz), 7.01 (1H, d, J=8.5Hz), 7.10-7.20 (4H, m)

45 Reference Example 27

5-Methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

50 [0076] To a solution of 5-methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenol (0.19g) and 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoxy- α -D-glucopyranose (0.40g) in dichloromethane (15mL) was added boron trifluoride-diethyl ether complex (0.088mL) at 0°C, and the mixture was stirred for 20 minutes. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the organic layer was separated. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1) to give 5-methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.33g).

55 ¹H-NMR (CDCl_3) δ ppm: 1.85 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.85 (2H, t, J=7.1Hz), 3.30 (3H, s), 3.72 (2H, t, J=7.1Hz), 3.77

(3H, s), 3.75-3.85 (2H, m), 3.80-3.95 (1H, m), 4.19 (1H, dd, J=2.4, 12.2Hz), 4.25 (1H, dd, J=5.9, 12.2Hz), 4.60 (2H, s) , 5.07 (1H, d, J=7.7Hz), 5.10-5.20 (1H, m), 5.25-5.35 (2H, m), 6.53 (1H, dd, J=2.5, 8.7Hz), 6.65 (1H, d, J=2.5Hz), 6.94(1H, d, J=8.7Hz), 7.00-7.20 (4H, m)

5 Reference Example 28

Methyl 3-benzyloxy-4- (4-ethylbenzyl) benzoate

[0077] To a solution methyl 4-(4-ethylbenzyl)-3-hydroxybenzoate (1.28g) in *N,N*-dimethylformamide (14mL) were added potassium carbonate (0.98g) and benzyl bromide (0.62mL), and the mixture was stirred at room temperature for 19 hours. The reaction mixture was poured into water, and the mixture was extracted twice with diethyl ether. The combined organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate =5/1) to give methyl 3-benzyloxy-4-(4-ethylbenzyl)benzoate (1.6g).

15 ¹H-NMR (CDCl₃) δ ppm:

1.22 (3H, t, J=7.7Hz), 2.61 (2H, q, J=7.7Hz), 3.90 (3H, s) , 4.02 (2H, s), 5.11 (2H, s), 7.00-7.20 (5H, m), 7.25-7.40 (5H, m), 7.55-7.65 (2H, m)

20 Reference Example 29

3-Benzylbenzoic acid

[0078] Methyl 3-benzyloxy-4- (4-ethylbenzyl)benzoate (1.6g) was dissolved in a mixed solvent of tetrahydrofuran (5mL) and ethanol (5mL). To the solution was added 2 mol/Laqueous sodiumhydroxide solution (10mL), and the mixture was stirred at 80°C for 1 hour. The reaction mixture was cooled to ambient temperature, acidified with 2 mol/L hydrochloric acid, and the mixture was stirred under ice-cooling for 30 minutes. The resulting precipitated crystals were collected by filtration, washed with water and dried to give 3-benzyloxy-4-(4-ethylbenzyl)benzoic acid (1.4g)

25 ¹H-NMR (DMSO-d₆) δ ppm:

1.14 (3H, t, J=7.6Hz), 2.55 (2H, q, J=7.6Hz), 3.96 (2H, s) , 5.18 (2H, s), 7.05-7.15 (4H, m), 7.20-7.40 (6H, m), 7.50 (1H, dd, J=1.5, 7.9Hz), 7.55 (1H, d, J=1.5Hz), 12.84 (1H, s)

30 Example 9

5-Amino-2-(4-ethylbenzyl)phenol

[0079] To a solution of 3-benzyloxy-4-(4-ethylbenzyl)benzoic acid (1.4g) and triethylamine (1.3mL) in 1,4-dioxane (10mL) was added a solution of diphenylphosphoryl azide (1.3g) in 1,4-dioxane (10mL), and the mixture was stirred at 100°C for 1 hour. Benzyl alcohol (1.6mL) was added to the reaction mixture, and the mixture was stirred at the same temperature for 7 hours. The solvent of the reaction mixture was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate =4/1) to give benzyl *N*-(3-benzyloxy-4-(4-ethylbenzyl)phenyl)carbamate (1.4g). To a solution of obtained benzyl *N*-(3-benzyloxy-4-(4-ethylbenzyl)phenyl)carbamate (1.4g) in methanol (15mL) was added 10% palladium-carbon powder (0.28g), and the mixture was stirred under a hydrogen atmosphere for 11 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate =1/1) to give 5-amino-2- (4-ethylbenzyl) phenol (0.54g).

40 ¹H-NMR (CDCl₃) δ ppm:

1.21 (3H, t, J=7.7Hz), 2.61 (2H, q, J=7.7Hz), 3.56 (2H, brs), 3.85 (2H,s), 4.57 (1H, s) , 6.18 (1H, d, J=2.4Hz), 6.25 (1H, dd, J=2.4, 8.1Hz), 6.89 (1H, d, J=8.1Hz), 7.05-7.15 (4H, m)

45 50 Example 10

Benzyl *N*-[4-(4-ethylbenzyl)-3-hydroxyphenyl]carbamate

[0080] To a solution of 5-amino-2-(4-ethylbenzyl)phenol (0.25g) in tetrahydrofuran (10mL) was added *N*-benzyloxy-carbonyloxy-succinimide (0.41g), and the mixture was stirred at room temperature for 22 hours. The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1) to give benzyl *N*-[4-(4-ethylbenzyl)-3-hydroxyphenyl]carbamate (0.40g).

55 ¹H-NMR (CDCl₃) δ ppm:

1.21 (3H, t, J=7.7Hz), 2.60 (2H, q, J=7.7Hz), 3.90 (2H, s), 5.00 (1H, brs), 5.19 (2H, s), 6.59 (1H, brs), 6.70 (1H, dd, J=2.3, 8.2Hz), 7.01 (1H, d, J=8.2Hz), 7.05-7.20 (5H, m), 7.30-7.45 (5H, m)

Reference Example 30

5

5-Benzylloxycarbonylamino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

[0081] The title compound was prepared in a similar manner to that described in Reference Example 27 using benzyl N-[4-(4-ethylbenzyl)-3-hydroxyphenyl]carbamate instead of 5-methoxy-2-(4-(2-methoxymethoxy)ethylbenzyl)phenol.

10

1 H-NMR ($CDCl_3$) δ ppm:

1.19 (3H, t, J=7.5Hz), 1.85 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.59 (2H, q, J=7.5Hz), 3.70-3.95 (3H, m), 4.10-4.40 (2H, m), 5.00-5.40 (6H, m), 6.63 (1H, brs), 6.74 (1H, dd, J=1.9, 8.2Hz), 6.95 (1H, d, J=8.2Hz), 6.95-7.10 (4H, m), 7.20-7.60 (6H, m)

15

Reference Example 31

5-Amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

20

[0082] To a solution of 5-benzylloxycarbonylamino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.35g) in tetrahydrofuran (4mL) was added 10% palladium-carbon powder (0.07g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 8 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 2/3 - dichloromethane/ethyl acetate = 1/1) to give 5-amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.19g).

25

1 H-NMR ($CDCl_3$) δ ppm:

1.19 (3H, t, J=7.6Hz), 1.84 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 2.59 (2H, q, J=7.6Hz), 3.59 (2H, brs), 3.70-3.90 (3H, m), 4.18 (1H, dd, J=2.5, 12.2Hz), 4.28 (1H, dd, J=5.3, 12.2Hz), 5.04 (1H, d, J=7.5Hz), 5.10-5.35 (3H, m), 6.34 (1H, dd, J=2.1, 8.0Hz), 6.42 (1H, d, J=2.1Hz), 6.82 (1H, d, J=8.0Hz), 6.95-7.15 (4H, m)

30

Reference Example 32

2-(Methoxymethoxy)-4,6-dimethylbenzaldehyde

35

[0083] To a solution of 2-hydroxy-4,6-dimethylbenzaldehyde (0.75g) and *N,N*-diisopropylethylamine (1.4mL) in dichloromethane (20mL) was added chloromethyl methyl ether (0.57mL), and the mixture was stirred at room temperature for 24 hours. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 20/1) to give 2-(methoxymethoxy)-4,6-dimethylbenzaldehyde (0.57g).

40

1 H-NMR ($CDCl_3$) δ ppm:

2.34 (3H, s), 2.55 (3H, s), 3.51 (3H, s), 5.26 (2H, s), 6.65-6.70 (1H, m), 6.85-6.90 (1H, m), 10.61 (1H, s)

45

Reference Example 33

4'--(3-Benzylxypropyl)-2-(methoxymethoxy)-4,6-dimethylphenylmethanol

50

[0084] A Grignard reagent was prepared from 1-(3-benzylxypropyl)-4-bromobenzene (1.3g), magnesium (0.11g), a catalytic amount of iodine and tetrahydrofuran (4.4mL). To the obtained Grignard reagent solution was added a solution of 2-(methoxymethoxy)-4,6-dimethylbenzaldehyde (0.57g) in tetrahydrofuran (10mL), and the mixture was stirred for 20 minutes. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 4'-(3-benzylxypropyl)-2-(methoxymethoxy)-4,6-dimethylphenylmethanol (1.1g).

55

1 H-NMR ($CDCl_3$) δ ppm:

1.80-1.95 (2H, m), 2.31 (3H, s), 2.32 (3H, s), 2.60-2.75 (2H, m), 3.12 (3H, s), 3.46 (2H, t, J=6.2Hz), 3.91 (1H, d, J=10.7Hz), 4.49 (2H, s), 4.93 (1H, d, J=6.5Hz), 5.03 (1H, d, J=6.5Hz), 6.03 (1H, d, J=10.7Hz), 6.70-6.75 (1H, m),

6.75-6.80 (1H, m), 7.05-7.10 (2H, m), 7.15-7.20 (2H, m), 7.20-7.40 (5H, m)

Reference Example 34

5 4'-(3-Hydroxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane

[0085] To a solution of 4'-(3-benzyloxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethanol (1.1g) in ethanol (27mL) was added 10% palladium-carbon powder (0.46g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 17 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure to give 4'-(3-hydroxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane (0.85g).

¹⁰ ¹H-NMR (CDCl₃) δ ppm:

1.80-1.90 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.60-2.70 (2H, m), 3.36 (3H, s), 3.60-3.70 (2H, m), 4.00 (2H, s), 5.13 (2H, s), 6.65-6.70 (1H, m), 6.75-6.85 (1H, m), 7.00-7.10 (4H, m)

15

Reference Example 35

4'-(3-Benzoyloxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane

20 [0086] To a solution of 4'-(3-hydroxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane (0.85g), triethylamine (0.49mL), and 4-(dimethylamino)pyridine (0.033g) in dichloromethane (14mL) was added benzyl chloride (0.38mL), and the mixture was stirred at room temperature for 18 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 20/1) to give 4'-(3-benzoyloxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane (1.1g).

¹H-NMR (CDCl₃) δ ppm:

2.00-2.10 (2H, m), 2.20 (3H, s), 2.30 (3H, s), 2.65-2.75 (2H, m), 3.36 (3H, s), 4.00 (2H, s), 4.25-4.35 (2H, m), 5.13 (2H, s), 6.65-6.70 (1H, m), 6.75-6.85 (1H, m), 7.00-7.10 (4H, m), 7.40-7.50 (2H, m), 7.50-7.60 (1H, m), 8.00-8.10 (2H, m)

30

Example 11

2-[4-(3-Benzoyloxypropyl)benzyl]-3,5-dimethylphenol

35 [0087] To a solution of 4'-(3-benzoyloxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane (1.1g) in methanol (13mL) was added p-toluenesulfonic acid monohydrate (0.096g), and the mixture was stirred at 60°C for 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 6/1) to give 2-[4-(3-benzoyloxypropyl)-benzyl]-3,5-dimethylphenol (0.89g).

40 ¹H-NMR (CDCl₃) δ ppm:

2.00-2.10 (2H, m), 2.23 (3H, s), 2.26 (3H, s), 2.65-2.80 (2H, m), 3.98 (2H, s), 4.25-4.35 (2H, m), 4.53 (1H, s), 6.45-6.55 (1H, m), 6.60-6.70 (1H, m), 7.00-7.15 (4H, m), 7.40-7.50 (2H, m), 7.50-7.60 (1H, m), 8.00-8.10 (2H, m)

45

Example 36

4'-(2-Benzylxyethyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethanol

50 [0088] The title compound was prepared in a similar manner to that described in Reference Example 33 using 1-(2-benzylxyethyl)-4-bromobenzene instead of 1-(3-benzyloxypropyl)-4-bromobenzene.

¹H-NMR (CDCl₃) δ ppm:

2.30 (3H, s), 2.32 (3H, s), 2.89 (2H, t, J=7.3Hz), 3.13 (3H, s), 3.64 (2H, t, J=7.3Hz), 3.89 (1H, d, J=10.7Hz), 4.50 (2H, s), 4.93 (1H, d, J=6.6Hz), 5.02 (1H, d, J=6.6Hz), 6.03 (1H, d, J=10.7Hz), 6.70-6.75 (1H, m), 6.75-6.80 (1H, m), 7.10-7.35 (9H, m)

55

Reference Example 37

4'-(2-hydroxyethyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane

5 [0089] The title compound was prepared in a similar manner to that described in Reference Example 34 using 4'-(2-benzyloxyethyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethanol instead of 4'-(3-benzyloxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethanol.

10 ¹H-NMR (CDCl₃) δ ppm: 1.31 (1H, t, J=5.9Hz), 2.20 (3H, s), 2.30 (3H, s), 2.80 (2H, t, J=6.5Hz), 3.37 (3H, s), 3.75-3.85 (2H, m), 4.01 (2H, s), 5.13 (2H, s), 6.65-6.70 (1H, m), 6.75-6.85 (1H, m), 7.05-7.10 (4H, m)

Reference Example 38

4'-(2-Benzoyloxyethyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane

15 [0090] The title compound was prepared in a similar manner to that described in Reference Example 35 using 4'-(2-hydroxyethyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane instead of 4'-(3-hydroxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane.

20 ¹H-NMR (CDCl₃) δ ppm: 2.19 (3H, s), 2.30 (3H, s), 3.01 (2H, t, J=7.0Hz), 3.33 (3H, s), 4.01 (2H, s), 4.47 (2H, t, J=7.0Hz), 5.11 (2H, s), 6.65-6.70 (1H, m), 6.75-6.85 (1H, m), 7.00-7.10 (2H, m), 7.10-7.15 (2H, m), 7.35-7.45 (2H, m), 7.50-7.60 (1H, m), 7.95-8.05 (2H, m)

Example 12

25 2-[4-(2-Benzoyloxyethyl)benzyl]-3,5-dimethylphenol

[0091] The title compound was prepared in a similar manner to that described in Example 11 using 4'-(2-benzoyloxyethyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane instead of 4'-(3-benzyloxypropyl)-2-(methoxymethoxy)-4,6-dimethyldiphenylmethane.

30 ¹H-NMR (CDCl₃) δ ppm: 2.22 (3H, s), 2.25 (3H, s), 3.02 (2H, t, J=7.0Hz), 3.99 (2H, s), 4.49 (2H, t, J=7.0Hz), 4.60 (1H, brs), 6.45-6.55 (1H, m), 6.60-6.65 (1H, m), 7.05-7.20 (4H, m), 7.35-7.45 (2H, m), 7.50-7.60 (1H, m), 7.95-8.05 (2H, m)

35 Reference Example 39

2-(4-Ethylbenzyl)-5-(methylamino)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

40 [0092] To a solution of 5-benzyloxycarbonylamino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.42g) and iodomethane (0.067mL) in tetrahydrofuran (7mL) was added sodium hydride (60%, 0.034g) at 0°C. The reaction mixture was warmed to ambient temperature and stirred for another 5 hours. Iodomethane (0.13mL) and sodium hydride (60%, 0.020g) were added to the reaction mixture, and the mixture was stirred for additional 1 hour. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on aminopropyl silica gel (eluent: hexane/ethyl acetate = 2/1) to give 5-(N-benzyloxycarbonyl-N-methyl)amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.30g). To a solution of the obtained 5-(N-benzyloxycarbonyl-N-methyl)amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.30g) in tetrahydrofuran (5mL) was added 10% palladium-carbon powder (0.060g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 6 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1) to give 2-(4-ethylbenzyl)-5-(methylamino)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.15g).

45 ¹H-NMR (CDCl₃) δ ppm: 1.19 (3H, t, J=7.7Hz), 1.84 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.58 (2H, q, J=7.7Hz), 2.81 (3H, s), 3.65 (1H, brs), 3.70-3.95 (3H, m), 4.18 (1H, dd, J=2.5, 12.3Hz), 4.26 (1H, dd, J=5.0, 12.3Hz), 5.07 (1H, d, J=7.7Hz), 5.10-5.20 (1H, m), 5.20-5.35 (2H, m), 6.28 (1H, dd, J=2.3, 8.2Hz), 6.36 (1H, d, J=2.3Hz), 6.85 (1H, d, J=8.2Hz), 7.00-7.10 (4H, m)

Example 13

4-(4-Ethylbenzyl)-3-hydroxybenzamide

5 [0093] To a mixture of methyl 4-(4-ethylbenzyl)-3-hydroxybenzoate (0.20g) and 28% aqueous ammonia solution (6mL) in ethanol (3mL) was added ammonium chloride (0.079g), and the mixture was stirred in sealed tube at 100°C for 14 hours. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. A mixed solvent of dichloromethane and methanol (10:1) was added to the residue, and an insoluble material was collected by filtration and dried to give 4-(4-ethylbenzyl)-3-hydroxybenzamide (0.065g).

10 $^1\text{H-NMR}$ (DMSO-d₆) δ ppm:

15.14 (3H, t, J=7.6Hz), 2.54 (2H, q, J=7.6Hz), 3.85 (2H, s), 7.00-7.15 (6H, m), 7.21 (1H, dd, J=1.7, 7.8Hz), 7.29 (1H, d, J=1.7Hz), 7.72 (1H, brs), 9.56 (1H, s)

Reference Example 40

5-Carbamoyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

20 [0094] The title compound was prepared in a similar manner to that described in Reference Example 27 using 4-(4-ethylbenzyl)-3-hydroxybenzamide instead of 5-methoxy-2-[2-(methoxymethoxy)ethyl]benzylphenol.

$^1\text{H-NMR}$ (CD₃OD) δ ppm:

1.19 (3H, t, J=7.6Hz), 1.85 (3H, s), 1.99 (3H, s), 2.04 (6H, s), 2.56 (2H, q, J=7.6Hz), 3.80-4.00 (2H, m), 4.00-4.35 (3H, m), 5.05-5.20 (1H, m), 5.20-5.30 (1H, m), 5.30-5.45 (2H, m), 6.95-7.20 (5H, m), 7.40-7.55 (1H, m), 7.55-7.65 (1H, m)

Reference Example 41

2-Hydroxy-4-(methoxymethoxy)benzaldehyde

30 [0095] To a suspension of 2,4-dihydroxybenzaldehyde (0.83g) and cesium carbonate (1.7g) in acetonitrile (30mL) was added chloromethyl methyl ether (0.55mL), and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 2-hydroxy-4-(methoxymethoxy)benzaldehyde (0.84g).

35 $^1\text{H-NMR}$ (CDCl₃) δ ppm:

3.48 (3H, s), 5.22 (2H, s), 6.60 (1H, d, J=2.2Hz), 6.65 (1H, dd, J=2.2,8.6Hz), 7.45 (1H, d, J=8.6Hz), 9.74 (1H, s), 11.37 (1H, s)

Reference Example 42

4'-Ethyl-2-hydroxy-4-(methoxymethoxy)diphenylmethanol

45 [0096] To a solution of 1-bromo-4-ethylbenzene (0.46g) in tetrahydrofuran (12mL) was added *tert*-butyl lithium (1.45 mol/L pentane solution, 1.9mL) under an argon atmosphere at -78°C, and the mixture was stirred for 30 minutes. To the reaction mixture was added a solution of 2-hydroxy-4-methoxymethoxybenzaldehyde (0.18g) in tetrahydrofuran (6mL). The mixture was warmed to 0°C and stirred for additional 15 minutes. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) to give 4'-ethyl-2-hydroxy-4-(methoxymethoxy)diphenylmethanol (0.30g).

50 $^1\text{H-NMR}$ (CDCl₃) δ ppm:

1.23 (3H, t, J=7.5Hz), 2.64 (2H, q, J=7.5Hz), 2.80 (1H, d, J=3.1Hz), 3.45 (3H, s), 5.12 (2H, s), 5.95 (1H, d, J=3.1Hz), 6.47 (1H, dd, J=2.5, 8.5Hz), 6.61 (1H, d, J=2.5Hz), 6.72 (1H, d, 8,5Hz), 7.15-7.25 (2H, m), 7.25-7.35 (2H, m), 8.07 (1H, s)

55

Example 14

2-(4-Ethylbenzyl)-5-(methoxymethoxy)phenol

5 [0097] To a solution of 4'-ethyl-2-hydroxy-4-(methoxymethoxy)diphenylmethanol (0.14g) in ethanol (5mL) was added 10% palladium-carbon powder (0.058g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hour. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 2-(4-ethylbenzyl)-5-(methoxymethoxy)phenol (0.12g).

10 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.21 (3H, t, $J=7.6\text{Hz}$), 2.61 (2H, q, $J=7.6\text{Hz}$), 3.47 (3H, s), 3.90 (2H, s), 4.73 (1H, s), 5.13 (2H, s), 6.53 (1H, d, $J=2.2\text{Hz}$),
6.58 (1H, dd, $J=2.2, 8.1\text{Hz}$), 7.02 (1H, d, $J=8.1\text{Hz}$), 7.10-7.15 (4H, m)

Reference Example 43

2-(4-Ethylbenzyl)-5-(methoxymethoxy)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

15 [0098] The title compound was prepared in a similar manner to that described in Reference Example 27 using 2-(4-ethylbenzyl)-5-(methoxymethoxy) phenol instead of 5-methoxy-2-(4-[2-(methoxymethoxy)ethyl]benzyl)phenol.

20 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.19 (3H, t, $J=7.6\text{Hz}$), 1.85 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.59 (2H, q, $J=7.6\text{Hz}$), 3.46 (3H, s), 3.79
25 (1H, d, $J=15.5\text{Hz}$), 3.84 (1H, d, $J=15.5\text{Hz}$), 3.85-3.95 (1H, m), 4.19 (1H, dd, $J=2.3, 12.2\text{Hz}$), 4.27 (1H, dd, $J=5.5, 12.2\text{Hz}$),
5.05-5.25 (4H, m), 5.25-5.40 (2H, m), 6.69 (1H, dd, $J=2.4, 8.4\text{Hz}$), 6.68 (1H, d, $J=2.4\text{Hz}$), 6.96 (1H, d, $J=8.4\text{Hz}$),
7.00-7.15 (4H, m)

Example 15

2-(4-Methoxybenzyl)-3,5-dimethylphenol

30 [0099] To 3,5-dimethylphenol (12g) were added lithium hydroxide monohydrate (4.2g) and 4-methoxybenzyl chloride (14mL) at 85°C, and the mixture was stirred 1.5 hours. The reaction mixture was cooled to ambient temperature and purified by column chromatography on silica gel (eluent: dichloromethane) to give 2-(4-methoxybenzyl)-3,5-dimethylphenol (5.1g).

35 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
2.24 (3H, s), 2.26 (3H, s), 3.77 (3H, s), 3.94 (2H, s), 4.53 (1H, s), 6.45-6.55 (1H, m), 6.55-6.65 (1H, m), 6.75-6.85 (2H,
m), 7.00-7.10 (2H, m)

Reference Example 44

2- (4-Methoxybenzyl)-3,5-dimethylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

40 [0100] To a solution of 2-(4-methoxybenzyl)-3,5-dimethylphenol (4.0g) and 2,3,4,6-tetra-O-acetyl-1-O-trichloroacetoimidoyl- α -D-glucopyranose (8.9g) in dichloromethane (100mL) was added boron trifluoride diethyl-ether complex (2.5mL) at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: dichloromethane). The solvent was removed under reduced pressure, ethanol was added to the residue, and the resulting crystals were collected by filtration. The obtained crystals were dried under reduced pressure to give 2-(4-methoxybenzyl)-3,5-dimethylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (7.8g).

45 $^1\text{H-NMR}$ (CDCl_3) δ ppm:
1.65 (3H, s), 2.00 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 2.30 (3H, s), 3.74 (3H, s), 3.78 (1H, d, $J=15.5\text{Hz}$),
3.80-3.95 (1H, m), 4.00 (1H, d, $J=15.5\text{Hz}$), 4.18 (1H, dd, $J=2.5, 12.2\text{Hz}$), 4.24 (1H, dd, $J=5.8, 12.2\text{Hz}$), 5.00-5.20 (2H,
m), 5.20-5.35 (2H, m), 6.70-6.80 (4H, m), 6.85-7.00 (2H, m)

Example 16

3-Hydroxy-4-(4-methoxybenzyl)benzamide

5 [0101] The title compound was prepared in a similar manner to that described in Example 13 using methyl 3-hydroxy-4-(4-methoxybenzyl)benzoate instead of methyl 4-(4-ethylbenzyl)-3-hydroxybenzoate. Purification was carried out by column chromatography on silica gel (eluent: dichloromethane/methanol = 8/1).

10 $^1\text{H-NMR}$ (CD_3OD) δ ppm:
3.74 (3H, s), 3.89 (2H, s), 6.75-6.85 (2H, m), 7.03 (1H, d, $J=7.8\text{Hz}$), 7.05-7.15 (2H, m), 7.21 (1H, dd, $J=1.6, 7.8\text{Hz}$),
7.27 (1H, d, $J=1.6\text{Hz}$)

Reference Example 45

3-Hydroxy-4-(4-methoxybenzyl)benzonitrile

15 [0102] To a solution of 3-hydroxy-4-(4-methoxybenzyl)benzamide (0.047g) and triethylamine (0.30mL) in dichloromethane (1.8mL) was added trifluoromethanesulfonic anhydride (0.34mL), and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The 20 organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol = 9/1) to give 3-hydroxy-4-(4-methoxybenzyl)benzonitrile (0.014g).

1H-NMR (CDCl_3) δ ppm:
3.80 (3H, s), 4.06 (2H, s), 6.80-6.90 (2H, m), 7.05-7.15 (2H, m), 7.25 (1H, d, $J=8.0\text{Hz}$), 7.66 (1H, dd, $J=1.6, 8.0\text{Hz}$),
7.76 (1H, d, $J=1.6\text{Hz}$)

25 Reference Example 46

5-Cyano-2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

30 [0103] The title compound was prepared in a similar manner to that described in Reference Example 27 using 3-hydroxy-4-(4-methoxybenzyl)benzonitrile instead of 5-methoxy-2-[4-(2-(methoxymethoxy)ethyl]benzylphenol.

1H-NMR (CDCl_3) δ ppm:
1.93 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.14 (3H, s), 3.78 (3H, s), 3.87 (2H, s), 3.90-4.00 (1H, m), 4.15-4.30 (2H, m),
5.05-5.20 (2H, m), 5.25-5.45 (2H, m), 6.75-6.90 (2H, m), 6.95-7.10 (2H, m), 7.10-7.20 (1H, m), 7.20-7.35 (2H, m)

35 Reference Example 47

2-Hydroxy-4,4'-dimethoxydiphenylmethanol

40 [0104] The title compound was prepared in a similar manner to that described in Reference Example 26 using 4-bromoanisole instead of 1-bromo-4-[2-(methoxymethoxy)ethyl]benzene.

1H-NMR (CDCl_3) δ ppm:
2.66 (1H, d, $J=3.0\text{Hz}$), 3.77 (3H, s), 3.81 (3H, s), 5.95 (1H, d, $J=3.0\text{Hz}$), 6.36 (1H, dd, $J=2.6, 8.5\text{Hz}$), 6.49 (1H, d,
 $J=2.6\text{Hz}$), 6.69 (1H, d, $J=8.5\text{Hz}$), 6.85-6.95 (2H, m), 7.25-7.35 (2H, m), 8.10 (1H, s)

45 Example 17

5-Methoxy-2-(4-methoxybenzyl)phenol

50 [0105] The title compound was prepared in a similar manner to that described in Example 8 using 2-hydroxy-4,4'-dimethoxydiphenylmethanol instead of 2-hydroxy-4-methoxy-4-[2-(methoxymethoxy)ethyl]diphenylmethanol.

1H-NMR (CDCl_3) δ ppm:
3.77 (3H, s), 3.78 (3H, s), 3.87 (2H, s), 4.67 (1H, s), 6.39 (1H, d, $J=2.5\text{Hz}$), 6.46 (1H, dd, $J=2.5, 8.3\text{Hz}$), 6.75-6.90 (2H,
m), 7.01 (1H, d, $J=8.3\text{Hz}$), 7.05-7.20 (2H, m)

55

Reference Example 48

5-Methoxy-2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

5 [0106] The title compound was prepared in a similar manner to that described in Reference Example 27 using 5-methoxy-2-(4-methoxybenzyl)phenol instead of 5-methoxy-2-(4-[2-(methoxymethoxy)ethyl]benzyl)phenol.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.88 (3H, s), 2.02 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.70-3.95 (9H, m), 4.19 (1H, dd, $J=2.5, 12.2\text{Hz}$), 4.25 (1H, dd, $J=5.9, 12.2\text{Hz}$), 5.07 (1H, d, $J=7.4\text{Hz}$), 5.10-5.40 (3H, m), 6.54 (1H, dd, $J=2.4, 8.4\text{Hz}$), 6.65 (1H, d, $J=2.4\text{Hz}$), 6.75-6.85 (2H, m), 6.94 (1H, d, $J=8.4\text{Hz}$), 7.00-7.10 (2H, m)

Reference Example 49

3-Benzylxyloxy-4-(4-ethylbenzyl)benzyl alcohol

15 [0107] To a solution of methyl 4-(4-ethylbenzyl)-3-hydroxybenzoate (1.3g) in *N,N*-dimethylformamide (15mL) were added potassium carbonate (0.79g) and benzyl bromide (0.62mL), and the mixture was stirred at room temperature for 13 hours. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (10mL). The resulting solution was added to a suspension of lithium aluminium hydride (0.57g) in diethyl ether (50mL) at 0°C, and the mixture was heated under reflux for 1.5 hours. The reaction mixture was cooled to 0°C, water (0.60mL), 15% aqueous sodium hydroxide solution (0.60mL) and water (1.8mL) were successively added to the reaction mixture, and the mixture was stirred for 5 minutes. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 2/1) to give 3-benzylxyloxy-4-(4-ethylbenzyl) benzyl alcohol (1.3g).

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.22 (3H, t, $J=7.7\text{Hz}$), 1.57 (1H, t, $J=6.2\text{Hz}$), 2.61 (2H, q, $J=7.7\text{Hz}$), 3.98 (2H, s), 4.65 (2H, d, $J=6.2\text{Hz}$), 5.07 (2H, s), 6.87 (1H, dd, $J=1.1, 7.5\text{Hz}$), 6.97 (1H, d, $J=1.1\text{Hz}$), 7.05-7.15 (5H, m), 7.25-7.40 (5H, m)

30 Reference Example 50

[3-Benzylxyloxy-4-(4-ethylbenzyl)phenyl]acetonitrile

35 [0108] To a solution of 3-benzylxyloxy-4-(4-ethylbenzyl)benzyl alcohol (0.87g) in dichloromethane (20mL) were added triethylamine (0.44mL) and methanesulfonyl chloride (0.22mL) at 0°C, and the mixture was stirred for 2 hours. To the reaction mixture was added 0.5 mol/L aqueous hydrochloric acid solution, and the mixture was extracted with diethyl ether. The organic layer was washed with water and a saturated aqueous sodium hydrogen carbonate solution, and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in dimethyl sulfoxide (10mL). To the solution were added potassium cyanide (0.68g) and a catalytic amount of sodium iodide, and the resulting mixture was stirred at 80°C for 12 hours. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1-3/1) to give [3-benzylxyloxy-4-(4-ethylbenzyl)phenyl] acetonitrile (0.41g).

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.22 (3H, t, $J=7.5\text{Hz}$), 2.61 (2H, q, $J=7.5\text{Hz}$), 3.70 (2H, s), 3.97 (2H, s), 5.07 (2H, s), 6.80-6.90 (2H, m), 7.05-7.15 (5H, m), 7.25-7.45 (5H, m)

50 Reference Example 51

2-[3-Benzylxyloxy-4-(4-ethylbenzyl)phenyl]acetamide

55 [0109] To a mixture of [3-benzylxyloxy-4-(4-ethylbenzyl)-phenyl] acetonitrile (0.41g) in ethanol (5mL) and water (10mL) was added potassium hydroxide (0.68g), and the mixture was heated under reflux for 4 hours. The reaction mixture was acidified by adding 2 mol/L aqueous hydrochloric acid solution, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give [3-benzylxyloxy-4-(4-ethylbenzyl)phenyl] acetic acid (0.41g). To a solution of the obtained

[3-benzyloxy-4-(4-ethylbenzyl)phenyl] acetic acid (0.41g) in tetrahydrofuran (10mL) were added pyridine (0.19mL), *tert*-butyl dicarbonate (0.50g) and ammonium hydrogen carbonate (0.18g), and the mixture was stirred at room temperature for 18 hours. To the reaction mixture was added 1 mol/L aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 2-[3-benzyloxy-4-(4-ethylbenzyl)phenyl]acetamide (0.38g).

5 ¹H-NMR (DMSO-d₆) δ ppm: 1.14 (3H, t, J=7.5Hz), 2.53 (2H, q, J=7.5Hz), 3.25-3.40 (2H, m), 3.85 (2H, s), 5.06 (2H, s), 6.78 (1H, dd, J=1.0, 7.9Hz),
10 6.84 (1H, brs), 6.98 (1H, d, J=1.0Hz), 7.00-7.10 (5H, m), 7.25-7.45 (6H, m)

Reference Example 52

2- [4- (4-Ethylbenzyl) -3-hydroxyphenyl] acetamide

15 [0110] To a solution of 2-[3-benzyloxy-4-(4-ethylbenzyl)-phenyl]acetamide (0.38g) in methanol (5mL) was added 10% palladium-carbon powder (0.075g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 hours. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 20/1-20/1) to give 2-[4-(4-ethylbenzyl)-3-hydroxyphenyl]acetamide (0.16g).

20 ¹H-NMR (DMSO-d₆) δ ppm: 1.13 (3H, t, J=7.6Hz), 2.53 (2H, q, J=7.6Hz), 3.22 (2H, s), 3.77 (2H, s), 6.59 (1H, dd, J=1.5, 7.7Hz), 6.72 (1H, d, J=1.5Hz), 6.81 (1H, brs), 6.90 (1H, d, J=7.7Hz), 7.00-7.15 (4H, m), 7.37 (1H, brs), 9.27 (1H, s)

25 Reference Example 53

5-Carbamoylmethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

30 [0111] The title compound was prepared in a similar manner to that described in Reference Example 27 using 2-[4-(4-ethylbenzyl)-3-hydroxyphenyl]acetamide instead of 5-methoxy-2-[2-(methoxymethoxy)ethyl] benzyl)phenol.

35 ¹H-NMR (CDCl₃) δ ppm: 1.20 (3H, t, J=7.6Hz), 1.88 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 2.60 (2H, q, J=7.6Hz), 3.53 (2H, s), 3.80-3.95 (3H, m), 4.15-4.30 (2H, m), 5.13 (1H, d, J=7.1Hz), 5.15-5.25 (1H, m), 5.25-5.40 (3H, m), 5.48 (1H, brs), 6.91 (1H, dd, J=1.4, 7.9Hz), 6.97 (1H, d, J=1.4Hz), 7.00-7.15 (5H, m)

Reference Example 54

2-Hydroxy-4'-methoxy-4-(methoxymethyl)diphenylmethanol

40 [0112] The title compound was prepared in a similar manner to that described in Reference Example 26 using 4-bromoanisole and 2-hydroxy-4-methoxymethylbenzaldehyde instead of 1-bromo-4-[2-(methoxymethoxy)ethyl]benzene and 2-hydroxy-4-methoxybenzaldehyde.

45 ¹H-NMR (CDCl₃) δ ppm: 2.71 (1H, d, J=3.1Hz), 3.37 (3H, s), 3.80 (3H, s), 4.39 (2H, s), 5.99 (1H, d, J=3.1Hz), 6.70-6.85 (2H, m), 6.85-6.95 (3H, m), 7.25-7.35 (2H, m), 7.98 (1H, s)

Example 18

50 2-(4-Methoxybenzyl)-5-methoxymethylphenol

55 [0113] To a solution of 2-hydroxy-4'-methoxy-4-(methoxymethyl)diphenylmethanol (0.17g) in ethanol (11mL) was added 10% palladium-carbon powder (0.051g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 30 minutes. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1-2/1) to give 2-(4-methoxybenzyl)-5-methoxymethylphenol (0.082g).

1H-NMR (CDCl₃) δ ppm: 3.38 (3H, s), 3.78 (3H, s), 3.92 (2H, s), 4.39 (2H, s), 4.77 (1H, s), 6.75-6.90 (4H, m), 7.00-7.20 (3H, m)

Reference Example 55

2-(4-Methoxybenzyl)-5-methoxymethylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

5 [0114] The title compound was prepared in a similar manner to that described in Reference Example 27 using 2-(4-methoxybenzyl)-5-methoxymethylphenol instead of 5-methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenol.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.90 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.08 (3H, s), 3.37 (3H, s), 3.77 (3H, s), 3.84 (2H, s), 3.85-3.95 (1H, m), 4.10-4.30 (2H, m), 4.30-4.50 (2H, m), 5.10-5.25 (2H, m), 5.25-5.40 (2H, m), 6.75-6.85 (2H, m), 6.90-7.10 (5H, m)

10

Reference Example 56

5-Methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenyl β -D-glucopyranoside

15 [0115] To a solution of 5-methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.13g) in methanol (8mL) was added 2 mol/L aqueous sodium hydroxide solution (0.50mL), and the mixture was stirred at room temperature for 25 minutes. The solvent was removed under reduced pressure, and the residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol = 7/1) to give 5-methoxy-2-{4-[2-(methoxymethoxy)ethyl]benzyl}phenyl β -D-glucopyranoside (0.053g).

20

$^1\text{H-NMR}$ (CD_3OD) δ ppm:

2.81 (2H, t, $J=6.9\text{Hz}$), 3.24 (3H, s), 3.30-3.55 (4H, m), 3.60-3.75 (3H, m), 3.75 (3H, s), 3.88 (1H, d, $J=15.0\text{Hz}$), 3.90 (1H, dd, $J=2.0, 12.0\text{Hz}$), 4.00 (1H, d, $J=15.0\text{Hz}$), 4.57 (2H, s), 4.85-4.95 (1H, m), 6.50 (1H, dd, $J=2.5, 8.3\text{Hz}$), 6.79 (1H, d, $J=2.5\text{Hz}$), 6.93 (1H, d, $J=8.3\text{Hz}$), 7.05-7.20 (4H, m)

25

Reference Example 57

5-[2-(Benzyl)oxy]ethoxy]-2-(4-ethylbenzyl)phenyl β -D-glucopyranoside

30 [0116] To a suspension of 2-(4-ethylbenzyl)-5-hydroxyphenyl β -D-glucopyranoside (0.039g) and cesium carbonate (0.098g) in *N,N*-dimethylformamide (1mL) was added (2-bromoethyl)benzyl ether (0.025mL), and the mixture was stirred at 50°C for 3.5 hours. The reaction mixture was cooled to ambient temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol = 6/1) to give 5-[2-(benzyloxy)ethoxy]-2-(4-ethylbenzyl)phenyl β -D-glucopyranoside (0.022g).

35

$^1\text{H-NMR}$ (CD_3OD) δ ppm:

1.18 (3H, t, $J=7.6\text{Hz}$), 2.57 (2H, q, $J=7.6\text{Hz}$), 3.30-3.55 (4H, m), 3.67 (1H, dd, $J=5.4, 12.1\text{Hz}$), 3.75-3.85 (2H, m), 3.86 (1H, d, $J=15.0\text{Hz}$), 3.88 (1H, dd, $J=2.0, 12.1\text{Hz}$), 3.98 (1H, d, $J=15.0\text{Hz}$), 4.05-4.15 (2H, m), 4.58 (2H, s), 4.80-4.90 (1H, m), 6.52 (1H, dd, $J=2.4, 8.5\text{Hz}$), 6.81 (1H, d, $J=2.4\text{Hz}$), 6.93 (1H, d, $J=8.5\text{Hz}$), 7.00-7.20 (4H, m), 7.20-7.40 (5H, m)

40

Example 19

(E)-2-[4-(3-hydroxy-1-prop-1-ene-1-yl)benzyl]phenyl β -D-glucopyranoside

45 [0117] To a suspension of lithium aluminium hydride (0.036g) in tetrahydrofuran (5mL) was added *(E)*-2-[4-(2-ethoxycarbonylvinyl)benzyl]phenyl β -D-glucopyranoside (0.035g) at 0°C, and the mixture was stirred for 1 hour. Ethyl acetate (10mL) was added to the reaction mixture, and the mixture was stirred for 30 minutes. To the reaction mixture were added water and dilute hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give *(E)*-2-[4-(3-hydroxy-1-prop-1-ene-1-yl)benzyl]phenyl β -D-glucopyranoside (0.028g).

50

$^1\text{H-NMR}$ (CD_3OD) δ ppm:

3.35-3.55 (4H, m), 3.69 (1H, dd, $J=5.0, 12.0\text{Hz}$), 3.88 (1H, dd, $J=1.8, 12.0\text{Hz}$), 3.96 (1H, d, $J=14.9\text{Hz}$), 4.09 (1H, d, $J=14.9\text{Hz}$), 4.15-4.25 (2H, m), 4.91 (1H, d, $J=7.5\text{Hz}$), 6.30 (1H, dt, $J=5.9, 16.0\text{Hz}$), 6.50-6.60 (1H, m), 6.85-7.25 (6H, m), 7.25-7.35 (2H, m)

55

Example 20

2-(4-Methoxycarbonylbenzyl)phenyl β -D-glucopyranoside

- 5 [0118] To a solution of 2-(4-methoxycarbonylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.066g) in methanol (5mL) was added sodium methoxide (0.006g), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 2-(4-methoxycarbonylbenzyl)phenyl β -D-glucopyranoside (0.040g).
¹H-NMR (CD₃OD) δ ppm:
10 3.30-3.55 (4H, m), 3.68 (1H, dd, J=5.4, 11.9Hz), 3.85-3.95 (4H, m), 4.05 (1H, d, J=14.8Hz), 4.19 (1H, d, J=14.8Hz), 4.91 (1H, d, J=7.2Hz), 6.90-7.00 (1H, m), 7.05-7.15 (1H, m), 7.15-7.20 (2H, m), 7.30-7.40 (2H, m), 7.85-7.95 (2H, m)

Example 21

2-(4-Allyloxybenzyl)phenyl β -D-glucopyranoside

- 15 [0119] To a solution of 2-(4-allyloxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.44g) in methanol (2.5mL) and tetrahydrofuran (1.5mL) was added sodium methoxide (28% methanol solution, 0.030mL), and the mixture was stirred at room temperature for 4 hours. The solvent of the reaction mixture was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 2-(4-allyloxybenzyl)phenyl β -D-glucopyranoside (0.23g).
¹H-NMR (CD₃OD) δ ppm:
20 3.30-3.55 (4H, m), 3.69 (1H, dd, J=4.9, 11.9Hz), 3.88 (1H, dd, J=2.0, 11.9Hz), 3.92 (1H, d, J=14.8Hz), 4.03 (1H, d, J=14.8Hz), 4.45-4.55 (2H, m), 4.91 (1H, d, J=7.4Hz), 5.15-5.25 (1H, m), 5.30-5.40 (1H, m), 5.95-6.10 (1H, m), 6.75-6.85 (2H, m), 6.85-6.95 (1H, m), 7.00-7.10 (1H, m), 7.10-7.20 (4H, m)

Example 22

2-[4-(2-Benzylbenzyl) phenyl β -D-glucopyranoside

- 30 [0120] To a solution of 2-[4-(2-benzylbenzyl)phenol (3.2g) and 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose (12g) in toluene (34mL) and dichloromethane (17mL) was added boron trifluoride diethyl-ether complex (3.8mL), and the mixture was stirred at room temperature for 14 hours. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (50mL), sodium methoxide (28% methanol solution, 0.39mL) was added to the solution, and the mixture was stirred at room temperature for 2.5 hours. The solvent of the reaction mixture was removed under reduced pressure, water was added to the residue, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 2-[4-(2-benzylbenzyl) phenyl β -D-glucopyranoside (3.4g).
¹H-NMR (CD₃OD) δ ppm:
35 2.84 (2H, t, J=7.0Hz), 3.35-3.55 (4H, m), 3.60-3.75 (3H, m), 3.88 (1H, dd, J=2.0, 12.0Hz), 3.96 (1H, d, J=14.9Hz),
40 4.07 (1H, d, J=14.9Hz), 4.48(2H, s), 4.91 (1H, d, J=7.4Hz), 6.85-6.95 (1H, m), 7.00-7.20 (7H, m), 7.20-7.35 (5H, m)

Example 23

2-(4-Carboxybenzyl)phenyl β -D-glucopyranoside

- 50 [0121] To a solution of 2-[4-(methoxycarbonyl)benzyl]phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.050g) in methanol (1mL) was added 2 mol/L aqueous sodium hydroxide solution (0.26mL), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was purified by column chromatography on benzenesulfonylpropyl silica gel (eluent: methanol) to give 2-(4-carboxybenzyl)phenyl β -D-gluco-pyranoside (0.038g).
55 ¹H-NMR (CD₃OD) δ ppm:
3.30-3.55 (4H, m), 3.69 (1H, dd, J=5.1, 12.1Hz), 3.88 (1H, dd, J=2.0, 12.1Hz), 4.04 (1H, d, J=14.8Hz), 4.19 (1H, d, J=14.8Hz), 4.85-5.00 (1H, m), 6.85-7.00 (1H, m), 7.05-7.15 (1H, m), 7.15-7.20 (2H, m), 7.30-7.40 (2H, m), 7.85-7.95 (2H, m)

Example 24

2-(4-Cyanomethylbenzyl)phenyl β -D-glucopyranoside

- 5 [0122] 2-(4-Cyanomethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl β -D-glucopyranoside was prepared in a similar manner to that described in Reference Example 8 using 4-(2-hydroxybenzyl)-phenylacetonitrile instead of methyl 4-(2-hydroxybenzyl)-benzoate. Then the title compound was prepared in a similar manner to that described in Example 2 using 2-(4-cyanomethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 2-(4-methoxycarbonylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside.
- 10 $^1\text{H-NMR}$ (CD_3OD) δ ppm: 3.35-3.55 (4H, m), 3.67 (1H, dd, $J=5.3, 12.1\text{Hz}$), 3.82 (2H, s), 3.88 (1H, dd, $J=2.1, 12.1\text{Hz}$), 3.99 (1H, d, $J=14.9\text{Hz}$), 4.12 (1H, d, $J=14.9\text{Hz}$), 4.91 (1H, d, $J=7.6\text{Hz}$), 6.85-7.00 (1H, m), 7.00-7.10 (1H, m), 7.10-7.20 (2H, m), 7.20-7.30 (4H, m)

15 Example 25

2-(4-Carbamoylbenzyl)phenyl β -D-glucopyranoside

- 20 [0123] To a suspension of 4-(2-hydroxybenzyl)benzamide (0.063g) and 1,2,3,4,6-penta-O-acetyl- β -D-glucopyranose (0.33g) in toluene (3mL) was added boron trifluoride diethyl-ether complex (0.11mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 4/1) to give 2-(4-carbamoylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside. To a solution of the obtained 2-(4-carbamoylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside in methanol (5mL) was added sodium methoxide (0.005g), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: ethyl acetate/ethanol = 5/1) to give 2-(4-carbamoylbenzyl)phenyl β -D-glucopyranoside (0.068g).
- 25 $^1\text{H-NMR}$ (CD_3OD) δ ppm: 3.30-3.55 (4H, m), 3.68 (1H, dd, $J=5.5, 11.9\text{Hz}$), 3.88 (1H, dd, $J=2.1, 11.9\text{Hz}$), 4.04 (1H, d, $J=14.9\text{Hz}$), 4.19 (1H, d, $J=14.9\text{Hz}$), 4.92 (1H, d, $J=7.5\text{Hz}$), 6.90-7.00 (1H, m), 7.05-7.15 (1H, m), 7.15-7.20 (2H, m), 7.30-7.40 (2H, m), 7.70-7.80 (2H, m)

Example 26

35 2-[4-(*N,N*-dimethylamino)benzyl]phenyl β -D-glucopyranoside

- 40 [0124] To a solution of 2-[4-(*N,N*-dimethylamino)benzyl]phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside (0.10g in methanol (2mL) and tetrahydrofuran (1mL) was added sodium methoxide (28% methanol solution, 0.007mL), and the mixture was stirred at room temperature for 70 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on aminopropyl silica gel (eluent: dichloromethane/methanol = 8/1) to give 2-[4-(*N,N*-dimethylamino)benzyl]phenyl β -D-glucopyranoside (0.069g).

45 $^1\text{H-NMR}$ (CD_3OD) δ ppm: 2.85 (6H, s), 3.35-3.55 (4H, m), 3.69 (1H, dd, $J=5.2, 12.0\text{Hz}$), 3.88 (1H, dd, $J=1.9, 12.0\text{Hz}$), 3.89 (1H, d, $J=15.0\text{Hz}$), 3.98 (1H, d, $J=15.0\text{Hz}$), 4.90 (1H, d, $J=7.6\text{Hz}$), 6.65-6.75 (2H, m), 6.85-6.95 (1H, m), 7.00-7.05 (1H, m), 7.05-7.10 (2H, m), 7.10-7.15 (2H, m)

Example 27

50 2-[(4-Benzyloxy)benzyl]phenyl β -D-glucopyranoside

- 55 [0125] The title compound was prepared in a similar manner to that described in Example 21 using 2-[4-(benzyloxy)benzyl]phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 2-(4-allyloxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside.

1H-NMR (CD_3OD) δ ppm: 3.35-3.55 (4H, m), 3.69 (1H, dd, $J=5.0, 12.0\text{Hz}$), 3.88 (1H, dd, $J=2.0, 12.0\text{Hz}$), 3.92 (1H, d, $J=14.8\text{Hz}$), 4.03 (1H, d, $J=14.8\text{Hz}$), 4.91 (1H, d, $J=7.3\text{Hz}$), 5.03 (2H, s), 6.80-6.95 (3H, m), 7.00-7.10 (1H, m), 7.10-7.20 (4H, m), 7.25-7.45 (5H, m)

Example 28

2-[4-(2-Hydroxyethyl)benzyl]-5-methoxyphenyl β -D-gluco-pyranoside

5 [0126] To a solution of 5-methoxy-2-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl β -D-glucopyranoside (0.053g) in methanol (2.3mL) was added *p*-toluenesulfonic acid monohydrate (0.032g), and the mixture was stirred at 50°C for 3 hours. The reaction mixture was cooled to ambient temperature, triethylamine (0.5mL) was added to the reaction mixture, and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol = 6/1) to give 2-[4-(2-hydroxyethyl)benzyl]-5-methoxyphenyl β -D-glucopyranoside (0.023g)

10 $^1\text{H-NMR}$ (CD_3OD) δ ppm:

2.76 (2H, t, $J=7.0\text{Hz}$), 3.30-3.55 (4H, m), 3.60-3.75 (3H, m), 3.75 (3H, s), 3.87 (1H, d, $J=15.0\text{Hz}$), 3.89 (1H, dd, $J=1.9, 12.2\text{Hz}$), 3.99 (1H, d, $J=15.0\text{Hz}$), 4.85-4.95 (1H, m), 6.50 (1H, dd, $J=2.5, 8.3\text{Hz}$), 6.78 (1H, d, $J=2.5\text{Hz}$), 6.94 (1H, d, $J=8.3\text{Hz}$), 7.05-7.20 (4H, m)

15

Example 29

5-Amino-2-(4-ethylbenzyl)phenyl β -D-glucopyranoside

20 [0127] To a solution of 5-amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranoside (0.19g) in methanol (3.5mL) was added sodium methoxide (28% methanol solution, 0.064mL), and the mixture was stirred at room temperature for 50 minutes. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The resulting precipitated crystals were collected by filtration, washed with water and dried under reduced pressure to give 5-amino-2-(4-ethylbenzyl)phenyl β -D-glucopyranoside (0.12g).

25 $^1\text{H-NMR}$ (CD_3OD) δ ppm:

1.18 (3H, t, $J=7.7\text{Hz}$), 2.57 (2H, q, $J=7.7\text{Hz}$), 3.30-3.50 (4H, m), 3.69 (1H, dd, $J=5.4, 12.0\text{Hz}$), 3.81 (1H, d, $J=15.0\text{Hz}$), 3.90 (1H, dd, $J=2.1, 12.0\text{Hz}$), 3.92 (1H, d, $J=15.0\text{Hz}$), 4.80-4.95 (1H, m), 6.33 (1H, dd, $J=2.2, 8.1\text{Hz}$), 6.59 (1H, d, $J=2.2\text{Hz}$), 6.78 (1H, d, $J=8.1\text{Hz}$), 7.00-7.15 (4H, m)

30 Example 30

2-[4-(3-Hydroxypropyl)benzyl]-3,5-dimethylphenyl β -D-glucopyranoside

35 [0128] To a solution of 2-[4-(3-benzyloxypropyl)benzyl]-3,5-dimethylphenol (0.72g) and 1,2,3,4,6-penta-*O*-acetyl- β -D-glucopyranose (2.3g) in toluene (7mL) and dichloromethane (3mL) was added boron trifluoride-diethyl ether complex (0.73mL), and the mixture was stirred at room temperature for 10 hours. Ethyl acetate and a saturated aqueous sodium hydrogen carbonate were added to the reaction mixture, and the organic layer was separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (6mL) and tetrahydrofuran (4mL). To the solution was added sodium

40 methoxide (28% methanol solution, 0.19m), and the mixture was stirred at 30°C for 7.5 hours. Ethyl acetate and water were added to the reaction mixture, and the organic layer was separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in methanol (10mL), sodium methoxide (28% methanol solution, 0.075mL) was added to the solution, and the mixture was stirred at 30°C for 14 hours. The reaction mixture was purified by column chromatography on silica

45 gel (eluent: dichloromethane/ methanol = 8/1). The solvent was removed under reduced pressure, diethyl ether was added to the residue, and the resulting precipitates were collected by filtration. The obtained solid was washed with diethyl ether and dried under reduced pressure to give 2-[4-(3-hydroxypropyl)benzyl]-3,5-dimethylphenyl β -D-glucopyranoside (0.58g).

50 $^1\text{H-NMR}$ (CD_3OD) δ ppm:

1.70-1.85 (2H, m), 2.13 (3H, s), 2.27 (3H, s), 2.55-2.65 (2H, m), 3.30-3.45 (4H, m), 3.45-3.60 (2H, m), 3.68 (1H, dd, $J=5.3, 11.9\text{Hz}$), 3.87 (1H, dd, $J=2.3, 11.9\text{Hz}$), 3.95 (1H, d, $J=15.5\text{Hz}$), 4.15 (1H, d, $J=15.5\text{Hz}$), 4.80-4.90 (1H, m), 6.65-6.70 (1H, m), 6.85-6.95 (1H, m), 6.95-7.10 (4H, m)

55 Example 31

2-[4-(2-Hydroxyethyl)benzyl]-3,5-dimethylphenyl β -D-glucopyranoside

[0129] The title compound was prepared in a similar manner to that described in Example 30 using 2-[4-(2-benzoy-

loxyethyl)benzyl]-3,5-dimethylphenol instead of 2-[4-(3-benzyloxypropyl) benzyl]-3,5-dimethylphenol.

¹H-NMR (CD₃OD) δ ppm:

2.13 (3H, s), 2.27 (3H, s), 2.74 (2H, t, J=7.0Hz), 3.30-3.45 (4H, m), 3.60-3.75 (3H, m), 3.86 (1H, dd, J=2.3, 11.9Hz), 3.95 (1H, d, J=15.4Hz), 4.16 (1H, d, J=15.4Hz), 4.80-4.90 (1H, m), 6.65-6.70 (1H, m), 6.85-6.95 (1H, m), 7.00-7.10 (4H, m)

5

Example 32

2-(4-Ethylbenzyl)-5-methylaminophenyl β-D-glucopyranoside

10

[0130] The title compound was prepared in a similar manner to that described in Example 29 using 2-(4-ethylbenzyl)-5-methylaminophenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 5-amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

¹H-NMR (CD₃OD) δ ppm:

15

1.18 (3H, t, J=7.6Hz), 2.57 (2H, q, J=7.6Hz), 2.73 (3H, s), 3.30-3.55 (4H, m), 3.68 (1H, dd, J=5.7, 12.1Hz), 3.75-4.00

(3H, m), 4.80-4.90 (1H, m), 6.25 (1H, dd, J=2.2, 8.2Hz), 6.51 (1H, d, J=2.2Hz), 6.81 (1H, d, J=8.2Hz), 7.00-7.15 (4H, m)

Example 33

20 5-Carbamoyl-2-(4-ethylbenzyl)phenyl β-D-glucopyranoside

[0131] To a solution of 5-carbamoyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.13g) in methanol (3mL) was added sodiummethoxide (28% methanol solution, 0.043mL), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was purified by column chromatography on benzenesulfonylpropyl 25 silica gel (eluent: methanol). Diethyl ether was added to the obtained compound, and the resulting precipitated solid was collected by filtration and dried under reduced pressure to give 5-carbamoyl-2-(4-ethylbenzyl)phenyl β-D-glucopyranoside (0.079g).

¹H-NMR (CD₃OD) δ ppm:

30

1.19 (3H, t, J=7.6Hz), 2.59 (2H, q, J=7.6Hz), 3.30-3.60 (4H, m), 3.70 (1H, dd, J=7.2, 12.1Hz), 3.91 (1H, dd, J=2.2, 12.1Hz), 4.00 (1H, d, J=15.0Hz), 4.10 (1H, d, J=15.0Hz), 5.01 (1H, d, J=7.4Hz), 7.05-7.20 (5H, m), 7.44 (1H, dd, J=1.7, 7.9Hz), 7.64 (1H, d, J=1.7Hz)

Example 34

35 2-(4-Ethylbenzyl)-5-(methoxymethoxy)phenyl β-D-glucopyranoside

[0132] The title compound was prepared in a similar manner to that described in Reference Example 56 using 2-(4-ethylbenzyl)-5-(methoxymethoxy)phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside instead of 5-methoxy-2-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

40

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.6Hz), 2.57 (2H, q, J=7.6Hz), 3.35-3.55 (7H, m), 3.69 (1H, dd, J=5.0, 12.2Hz), 3.80-3.95 (2H, m), 3.98 (1H, d, J=15.3Hz), 4.80-4.95 (1H, m), 5.05-5.20 (2H, m), 6.61 (1H, dd, J=2.4, 8.4Hz), 6.89 (1H, d, J=2.4Hz), 6.94 (1H, d, J=8.4Hz), 7.00-7.20 (4H, m)

45

Example 35

2-(4-Ethylbenzyl)-5-hydroxyphenyl β-D-glucopyranoside

50

[0133] The title compound was prepared in a similar manner to that described in Example 28 using 2-(4-ethylbenzyl)-5-(methoxymethoxy)phenyl β-D-glucopyranoside instead of 5-methoxy-2-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl β-D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

55

1.18 (3H, t, J=7.6Hz), 2.57 (2H, q, J=7.6Hz), 3.35-3.55 (4H, m), 3.65-3.75 (1H, m), 3.83 (1H, d, J=15.1Hz), 3.85-3.95 (1H, m), 3.94 (1H, d, J=15.1Hz), 4.80-4.90 (1H, m), 6.37 (1H, dd, J=2.4, 8.2Hz), 6.64 (1H, d, J=2.4Hz), 6.84 (1H, d, J=8.2Hz), 7.00-7.15 (4H, m)

Example 36

2-(4-Ethylbenzyl)-5-(2-hydroxyethoxy)phenyl β -D-glucopyranoside

[0134] To a solution of 5-[2-(benzyloxy)ethoxy]-2-(4-ethylbenzyl)phenyl β -D-glucopyranoside (0.022g) in ethanol (1mL) was added 10% palladium-carbon powder (0.0082g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 1 hour. An insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol = 6/1) to give 2-(4-ethylbenzyl)-5-(2-hydroxyethoxy)phenyl β -D-glucopyranoside (0.013g).

1 H-NMR (CD_3OD) δ ppm:

1.18 (3H, t, $J=7.6Hz$), 2.57 (2H, q, $J=7.6Hz$), 3.30-3.55 (4H, m), 3.68 (1H, dd, $J=5.5, 12.1Hz$), 3.80-3.95 (4H, m), 3.95-4.05 (3H, m), 4.85-4.90 (1H, in), 6.53 (1H, dd, $J=2.3, 8.4Hz$), 6.81 (1H, d, $J=2.3Hz$), 6.93 (1H, d, $J=8.4Hz$), 7.00-7.15 (4H, m)

15

Example 37

2-(4-Methoxybenzyl)-3,5-dimethylphenyl β -D-glucopyranoside

[0135] To a suspension of 2-(4-methoxybenzyl)-3,5-dimethylphenyl 2,3,4, 6-tetra-O-acetyl- β -D-glucopyranoside (7.4g) in ethanol (150mL) was added 2 mol/L aqueous sodium hydroxide solution (65mL), and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 2-(4-methoxybenzyl)-3,5-dimethylphenyl (β -D-glucopyranoside (5.2g).

25

1 H-NMR (CD_3OD) δ ppm:

2.13 (3H, s), 2.27 (3H, s), 3.30-3.50 (4H, m), 3.60-3.75 (4H, m), 3.80-4.00 (2H, m), 4.00-4.20 (1H, m), 4.80-4.90 (1H, m), 6.60-6.80 (3H, m), 6.85-6.95 (1H, m), 7.00-7.10 (2H, m)

30

Example 38

5-Cyano-2-(4-methoxybenzyl)phenyl β -D-glucopyranoside

[0136] The title compound was prepared in a similar manner to that described in Reference Example 74 using 5-cyano-2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 5-methoxy-2-[4-(2-methoxymethoxyethoxy)ethyl]benzylphenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside.

1 H-NMR (CD_3OD) δ ppm:

3.30-3.45 (1H, m), 3.45-3.60 (3H, m), 3.69 (1H, dd, $J=5.9, 12.2Hz$), 3.75 (3H, s), 3.91 (1H, dd, $J=2.2, 12.2Hz$), 3.98 (1H, d, $J=15.1Hz$), 4.07 (1H, d, $J=15.1Hz$), 4.99 (1H, d, $J=7.4Hz$), 6.75-6.85 (2H, m), 7.10-7.20 (2H, m), 7.19 (1H, d, $J=7.7Hz$), 7.28 (1H, dd, $J=1.4, 7.7Hz$), 7.49 (1H, d, $J=1.4Hz$)

40

Example 39

5-Methoxy-2-(4-methoxybenzyl)phenyl β -D-glucopyranoside

[0137] The title compound was prepared in a similar manner to that described in Example 29 using 5-methoxy-2-(4-methoxybenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 5-amino-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside

1 H-NMR (CD_3OD) δ ppm:

3.30-3.55 (4H, m), 3.68 (1H, dd, $J=5.8, 12.0Hz$), 3.74 (3H, s), 3.75 (3H, s), 3.80-4.00 (3H, m), 4.80-4.95 (1H, m), 6.50 (1H, dd, $J=2.4, 8.4Hz$), 6.70-6.85 (3H, m), 6.93 (1H, d, $J=8.4Hz$), 7.05-7.20 (2H, m)

50

Example 40

5-Carbamoylmethyl-2-(4-ethylbenzyl)phenyl β -D-glucopyranoside

55

[0138] The title compound was prepared in a similar manner to that described in Example 33 using 5-carbamoylmethyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside instead of 5-carbamoyl-2-(4-ethylbenzyl)phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside.

¹H-NMR (CD₃OD) δ ppm:

1.18 (3H, t, J=7.5Hz), 2.57 (2H, q, J=7.5Hz), 3.30-3.55 (6H, m), 3.69 (1H, dd, J=5.7, 12.2Hz), 3.90 (1H, dd, J=2.2, 12.2Hz), 3.92 (1H, d, J=14.6Hz), 4.03 (1H, d, J=14.6Hz), 4.93 (1H, d, J=7.6Hz), 6.87 (1H, dd, J=1.4, 7.6Hz), 7.00 (1H, d, J=7.6Hz), 7.00-7.20 (5H, m)

5

Example 41

5-[3-(Ethoxycarbonyl)propyloxy]-2-(4-ethylbenzyl)phenyl β-D-glucopyranoside

[0139] To a suspension of 2-(4-ethylbenzyl)-5-hydroxyphenyl β-D-glucopyranoside (0.051g) and cesium carbonate (0.13g) in N,N-dimethylformamide (2mL) was added ethyl 4-bromobutyrate (0.028mL), and the mixture was stirred at 50°C for 1 hour. The reaction mixture was cooled to ambient temperature, water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/methanol = 9/1) to give 5-[3-(ethoxycarbonyl)propyloxy]-2-(4-ethylbenzyl)phenyl β-D-glucopyranoside (0.028g).

¹H-NMR (CD₃OD) δ ppm:

1.18 (3H, t, J=7.6Hz), 1.23 (3H, t, J=7.1Hz), 1.95-2.10 (2H, m), 2.48 (2H, t, J=7.5Hz), 2.57 (2H, q, J=7.6Hz), 3.30-3.55 (4H, m), 3.68 (1H, dd, J=5.7, 12.1Hz), 3.80-4.05 (5H, m), 4.12 (2H, q, J=7.1Hz), 4.88 (1H, d, J=7.4Hz), 6.49 (1H, dd, J=2.4, 8.8Hz), 6.77 (1H, d, J=2.4Hz), 6.92 (1H, d, J=8.8Hz), 7.00-7.15 (4H, m)

Example 42

2-(4-Methoxybenzyl)-5-methoxymethylphenyl β-D-glucopyranoside

[0140] To a solution of 2-(4-methoxybenzyl)-5-methoxymethylphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.14g) in methanol (3mL) was added sodiummethoxide (28% methanol solution, 0.047mL), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was purified by column chromatography on benzenesulfonyl-propyl silica gel (eluent: methanol) to give 2-(4-methoxybenzyl)-5-methoxymethylphenyl β-D-glucopyranoside (0.084g).

¹H-NMR (CD₃OD) δ ppm:

3.35 (3H, s), 3.30-3.55 (4H, m), 3.69 (1H, dd, J=5.5, 12.1Hz), 3.74 (3H, s), 3.80-3.95 (2H, m), 4.01 (1H, d, J=15.0Hz), 4.35-4.45 (2H, m), 4.92 (1H, d, J=7.4Hz), 6.75-6.85 (2H, m), 6.90 (1H, dd, J=1.4, 7.7Hz), 7.02 (1H, d, J=7.7Hz), 7.10-7.20 (3H, m)

35

Test Example 1

Assay for inhibitory effect on human SGLT2 activity

40 1) Construction of the plasmid vector expressing human SGLT2

[0141] Preparation of the cDNA library for PCR amplification was performed by reverse transcription of a total RNA deprived from human kidney (Ori gene) with oligo dT as the primer, using SUPERSCRIPT Preamplification System (Gibco-BRL: LIFE TECHNOLOGIES). The DNA fragment coding for human SGLT2 was amplified by the PCR reaction, in which the human kidney cDNA library described above was used as the template and the following oligo nucleotides 0702F and 0712R, presented as Sequence Number 1 and 2 respectively, were used as the primers. The amplified DNA fragment was ligated into pCR-Blunt (Invitrogen), a vector for cloning, according to standard method of the kit. The *Escherichia coli* HB101 (Toyobo) was transformed according to usual method and then selection of the transformants was performed on the LB agar medium containing 50 µg/mL of kanamycin. After the plasmid DNA was extracted and purified from one of the transformants, amplifying of the DNA fragment coding for human SGLT2 was performed by the PCR reaction, in which the following oligo nucleotides 0714F and 0715R, presented as Sequence Number 3 and 4 respectively, were used as the primers. The amplified DNA fragment was digested with restriction enzymes, Xho I and Hind III, and then purified with Wizard Purification System (Promega). This purified DNA fragment was inserted at the corresponding restriction sites of pcDNA3.1 (-) Myc/His-B (Invitrogen), a vector for expressing of fusion protein. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformant was performed on the LB agar medium containing 100 µg/mL of ampicillin. After the plasmid DNA was extracted and purified from this transformant, the base sequence of the DNA fragment inserted at the multi-cloning sites of pcDNA3.1 (-) Myc/His-B was analyzed. This clone had a single base substitution (ATC which codes for the isoleucine-433 was substituted

by GTC) compared with the human SGLT2 reported by Wells *et al* (Am. J. Physiol., Vol. 263, pp. 459-465 (1992)). Sequentially, a clone in which valine is substituted for the isoleucine-433 was obtained. This plasmid vector expressing human SGLT2 in which the peptide presented as Sequence Number 5 is fused to the carboxyl terminal alanine residue was designated KL29.

5

	Sequence Number 1	ATGGAGGAGCACACAGAGGC
10	Sequence Number 2	GGCATAGAACCCCCAGAGGA
15	Sequence Number 3	AACCTCGAGATGGAGGAGCACACAGAGGC
20	Sequence Number 4	AACAAGCTTGGCATAGAACCCCCAGAGGA
	Sequence Number 5	KLGPEQKLISEEDLNSAVDHHHHHH

2) Preparation of the cells expressing transiently human SGLT2

25

[0142] KL29, the plasmid coding human SGLT2, was transfected into COS-7 cells (RIKEN CELL BANK RCB0539) by electroporation. Electroporation was performed with GENE PULSER II (Bio-Rad Laboratories) under the condition: 0.290 kV, 975 μ F, 2×10^6 cells of COS-7 cell and 20 μ g of KL29 in 500 μ L of OPTI-MEM I medium (Gibco-BRL : LIFE TECHNOLOGIES) in the 0.4 cm type cuvette. After the gene transfer, the cells were harvested by centrifugation and resuspended with OPTI-MEM I medium (1 mL/cuvette). To each well in 96-wells plate, 125 μ L of this cell suspension was added. After overnight culture at 37 °C under 5 % CO₂, 125 μ L of DMEM medium which is containing 10 % of fetal bovine serum (Sanko Jyunyaku), 100 units/mL sodium penicillin G (Gibco-BRL: LIFE TECHNOLOGIES), 100 μ g/mL streptomycin sulfate (Gibco-BRL: LIFE TECHNOLOGIES) was added to each well. After a culture until the following day, these cells were used for the measurement of the inhibitory activity against the uptake of methyl- α -D-glucopyranoside.

35

3) Measurement of the inhibitory activity against the uptake of methyl- α -D-glucopyranoside

40

[0143] After a test compound was dissolved in dimethyl sulfoxide and diluted with the uptake buffer (a pH 7.4 buffer containing 140 mM sodium chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 5 mM methyl- α -D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane), each diluent was used as test sample for measurement of the inhibitory activity. After removal of the medium of the COS-7 cells expressing transiently human SGLT2, to each well 200 μ L of the pretreatment buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane) was added, and the cells were incubated at 37°C for 10 minutes. After the pretreatment buffer was removed, 200 μ L of the same buffer was added again, and the cells were incubated at 37°C for 10 minutes. The buffer for measurement was prepared by adding of 7 μ L of methyl- α -D-(U-14C)-glucopyranoside (Amersham Pharmacia Biotech) to 525 μ L of the prepared test sample. For the control, the buffer for measurement without test compound was prepared. For estimate of the basal uptake in the absence of test compound and sodium, the buffer for measurement of the basal uptake, which contains 140 mM choline chloride in place of sodium chloride, was prepared similarly. After the pretreatment buffer was removed, 75 μ L of each buffer for measurement was added to each well, the cells were incubated at 37°C for 2 hours. After the buffer for measurement was removed, 200 μ L of the washing buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM methyl- α -D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane) was added to each well and immediately removed. After two additional washing, the cells were solubilized by addition of 75 μ L of 0.2 mol/L sodium hydroxide to each well. After the cell lysates were transferred to the PicoPlate (Packard) and 150 μ L of MicroScint-40 (Packard) was added to each well, the radioactivity

was measured with microplate scintillation counter TopCount (Packard). The difference in uptake was obtained as 100 % value by subtracting the radioactivity in the basal uptake from that in control and then the concentrations at which 50 % of uptake was inhibited (IC_{50} Value) were calculated from the concentration-inhibition curve by least square method. The results are shown in the following Table 1.

5

[Table 1]

Test compound	IC_{50} value (nM)
Example 19	120
Example 29	10
Example 30	30
Example 31	59
Example 37	290

10

15

Test Example 2

Assay for the facilitatory effect on urinary glucose excretion

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[0144] As experimental animals, overnight fasted SD rats (Japan SLC. Inc., male, 7 weeks of age, 180-220 g) were used. Ten mg of a test compound was suspended or dissolved in 300 μ L of ethanol and dissolved by adding 1.2 mL of polyethylene glycol 400 and 1.5 mL of saline to prepare a 3.3 mg/mL solution. A portion of this solution was diluted with a mixture (saline:polyethylene glycol 400:ethanol = 5:4:1) to prepare 3.3, 0.33 and 0.033 mg/mL solution. After body weights of the rats were measured, the solution of test compound was intravenously injected to the tail vein at a dose of 3mL/kg (10, 1, 0.1mg/kg). For control, only a mixture (saline:polyethylene glycol 400:ethanol = 5:4:1) was intravenously injected to the tail vein at a dose of 3 mL/kg. Immediately after intravenous injection to the tail vein, 200 g/L of aqueous glucose solution was orally administered to the rats at a dose of 10 mL/kg (2 g/kg). The intravenous injection to the tail vein was performed with 26 G injection needle and 1 mL syringe. The oral administration was performed with gastric tube for rat and 2.5 mL syringe. The head count in each group was 3. Collection of urine was performed in metabolic cage after the administration of glucose was finished. The sampling time for collection of urine was 24 hours after the administration of glucose. After the collection of urine was finished, the urine volume was recorded and the urinary glucose concentration was measured. The glucose concentration was measured with a kit for laboratory test: Glucose B-Test WAKO (Wako Pure Chemical Industries, Ltd.). The amount of urinary glucose excretion during 24 hours per 200 g of body weight was calculated from the urine volume, urinary glucose concentration and body weight. The results are shown in the following Table 2.

[Table 2]

Test compound	Dose (mg/kg)	Amount of Urinary Glucose Excretion (mg/24 hours/200g body weight)
Example 37	0.1	15
	1	125
	10	288

40

45

Test Example 3

Acute toxicity test

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[0145] A mixture (saline:polyethylene glycol 400:ethanol = 5:4:1) was added to a test compound to prepare 30 mg/mL solution. As experimental animals, 5 week old male ICR mice (CLEA JAPAN, INC. 29 - 35 g, 5 animals in each group), which were fasted for 4 hours, were used. The above solution was subcutaneously administered at a dose of 10 mL/kg (300 mg/kg) to the above experimental animals and then observation for 24 hours was performed. The results are shown in the following Table 3.

55

[Table 3]

Test compound	Death number
Example 37	0 / 5

5

Industrial Applicability

[0146] The glucopyranosyloxybenzylbenzene derivatives represented by the above general formula (I) and pharmaceutically acceptable salts thereof of the present invention have an inhibitory activity in human SGLT2 and exert an excellent hypoglycemic effect by excreting glucose in the urine through preventing the reabsorption of excess glucose at the kidney. Therefore, the present invention can provide agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complication or obesity by comprising as an active ingredient a glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof of the present invention.

[0147] In addition, compounds represented by the above general formula (II) of the present invention are important as intermediates for preparing the compounds represented by the above general formula (I) or pharmaceutically acceptable salts thereof, and therefore, the compounds represented by the above general formula (I) and pharmaceutically acceptable salts thereof can be readily prepared by way of these compounds.

20

[SEQUENCE LISTING FREE TEXT]

Sequence Number 1: Synthetic DNA primer

25

Sequence Number 2: Synthetic DNA primer

30

Sequence Number 3: Synthetic DNA primer

Sequence Number 4: Synthetic DNA primer

Sequence Number 5: Peptide fused to the carboxyl terminal
alanine residue of human SGLT2

35

40

45

50

55

SEQUENCE LISTING

5 <110> KISSEI PHARMACEUTICAL CO., LTD.
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 NISHIMURA, Toshihiro
 FUSHIMI, Nobuhiko
10 TATANI, Kazuya
 KIKUCHI, Norihiko
 KATSUNO, Kenji
 ISAJI, Masayuki

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 INTERMEDIATES THEREOF

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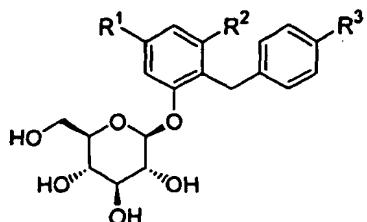
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 of human SGLT2
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 1 5 10 15
 45 Ala Val Asp His His His His His His
 20 25
 50 **Claims**

1. Aglucopyranosyloxybenzylbenzene derivative represented by the general formula:

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wherein R¹ represents a hydrogen atom, a hydroxy group, an amino group, a mono or di(lower alkyl)amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a lower alkoxy-substituted(lower alkyl) group, a lower alkoxy-substituted(lower alkoxy) group, a carbamoyl(lower alkyl) group, a lower alkoxy carbonyl-substituted(lower alkyl) group, a lower alkoxy carbonyl-substituted(lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted(lower alkyl) group, a lower alkoxy-substituted(lower alkoxy) group, a lower alkoxy-substituted(lower alkylthio) group, a lower alkenyloxy group, an aralkyloxy group, a hydroxy(lower alkenyl) group, a carboxy group, a lower alkoxy carbonyl group, a cyano group, an aralkyloxy(lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl(lower alkyl) group, an amino group, a mono or di(lower alkyl)amino group, a lower alkoxy carbonyl-substituted(lower alkyl) group, a lower alkoxy carbonyl-substituted(lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; with the proviso that R³ does not represent a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted(lower alkyl) group, a lower alkoxy-substituted(lower alkoxy) group or a lower alkoxy-substituted(lower alkylthio) group when R¹ represents a hydrogen atom or a hydroxy(lower alkyl) group and R² represents a hydrogen atom, or a pharmaceutically acceptable salt thereof.

2. A glucopyranosyloxybenzylbenzene derivative as claimed in claim 1 wherein R represents a hydrogen atom or a hydroxy (lower alkyl) group; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy (lower alkoxy) group, ahydroxy (lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a lower alkenyloxy group, an aralkyloxy group, a hydroxy(lower alkenyl) group, a carboxy group, a lower alkoxycarbonyl group, a cyano group, an aralkyloxy(lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (loweralkyl) group, an amino group, a mono or di(lower alkyl)amino group, a lower alkoxycarbonyl-substituted (lower alkyl) group, a lower alkoxycarbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; with the proviso that R³ does not represent a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy (lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group or a lower alkoxy-substituted (lower alkylthio) group when R¹ represents a hydrogen atom or a hydroxy(lower alkyl) group and R² represents a hydrogen atom, or a pharmaceutically acceptable salt thereof.
 3. A glucopyranosyloxybenzylbenzene derivative as claimed in claim 1 wherein R¹ represents a hydroxy group, an amino group, a mono or di (lower alkyl) amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a hydroxy (lower alkoxy) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl(lower alkyl) group, a lower alkoxycarbonyl-substituted (lower alkyl) group, a lower alkoxycarbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy (lower alkyl) group, a hydroxy (lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a lower alkenyloxy group, an aralkyloxy group, a hydroxy (lower alkenyl) group, a carboxy group, a lower alkoxycarbonyl group, a cyano group, an aralkyloxy (lower alkyl) group, a cyano (lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di (lower alkyl) amino group, a lower alkoxycarbonyl-substituted (lower alkyl) group, a lower alkoxycarbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group, or a pharmaceutically acceptable salt thereof.

4. A glucopyranosyloxybenzylbenzene derivative as claimed in claim 1 wherein R¹ represents a hydrogen atom, a hydroxy group, an amino group, a mono or di (lower alkyl) amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a hydroxy (lower alkyl) group, a hydroxy(lower alkoxy) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl(lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a lower alkenyloxy group, a hydroxy(lower alkenyl) group, a carbamoyl (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group or a carboxy (lower alkyl) group, or a pharmaceutically acceptable salt thereof.

5. A glucopyranosyloxybenzylbenzene derivative as claimed in claim 3 wherein R¹ represents an amino group, a mono or di (lower alkyl) amino group, a carbamoyl group, a carbamoyl (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; R² represents a hydrogen atom or a lower alkyl group; and R³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a hydroxy(lower alkyl) group, a hydroxy(lower alkoxy) group, a hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a lower alkenyloxy group, an aralkyloxy group, a hydroxy(lower alkenyl) group, a carboxy group, a lower alkoxy-carbonyl group, a cyano group, an aralkyloxy (lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, an amino group, a mono or di (lower alkyl) amino group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising as an active ingredient a glucopyranosyloxybenzylbenzene derivative as claimed in claim 1-5 or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition as claimed in claim 6 wherein the composition is a human SGLT2 inhibitor.

20. A pharmaceutical composition as claimed in claim 7 wherein the composition is an agent for the prevention or treatment of a disease associated with hyperglycemia.

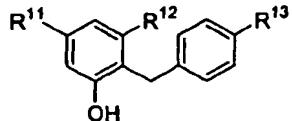
25. A pharmaceutical composition as claimed in claim 8 wherein a disease associated with hyperglycemia is diabetes or diabetic complication.

30. A pharmaceutical composition as claimed in claim 8 wherein a disease associated with hyperglycemia is obesity.

35. A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering a therapeutically effective amount of a glucopyranosyloxybenzylbenzene derivative as claimed in claim 1-5 or a pharmaceutically acceptable salt thereof.

40. A use of a glucopyranosyloxybenzylbenzene derivative as claimed in claim 1-5 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

45. A benzylphenol derivative represented by the general formula:



55 wherein R¹¹ represents a hydrogen atom, a protected hydroxy group, a protected amino group, a protected mono (lower alkyl)amino group, a di (lower alkyl) amino group, a carbamoyl group, a lower alkyl group, a lower alkoxy group, a protected hydroxy(lower alkyl) group, a protected hydroxy(lower alkoxy) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a carbamoyl (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower

alkyl) group or a carboxy(lower alkoxy) group; R¹² represents a hydrogen atom or a lower alkyl group; and R¹³ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a protected hydroxy(lower alkyl) group, a protected hydroxy(lower alkoxy) group, a protected hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group, a lower alkoxy-substituted (lower alkylthio) group, a lower alkenyloxy group, an aralkyloxy group, a protected hydroxy(lower alkenyl) group, a carboxy group, a lower alkoxycarbonyl group, a cyano group, an aralkyloxy(lower alkyl) group, a cyano(lower alkyl) group, a carbamoyl group, a carbamoyl (lower alkyl) group, a protected amino group, a protected mono(lower alkyl) amino group, a di(lower alkyl)amino group, a lower alkoxycarbonyl-substituted (lower alkyl) group, a lower alkoxy-carbonyl-substituted (lower alkoxy) group, a carboxy(lower alkyl) group or a carboxy(lower alkoxy) group; with the proviso that R¹³ does not represent a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a protected hydroxy(lower alkyl) group, a protected hydroxy(lower alkoxy) group, a protected hydroxy(lower alkylthio) group, a lower alkoxy-substituted (lower alkyl) group, a lower alkoxy-substituted (lower alkoxy) group or a lower alkoxy-substituted (lower alkylthio) group when R¹¹ represents a hydrogen atom or a protected hydroxy (lower alkyl) group and R¹² represents a hydrogen atom, or a salt thereof.

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INTERNATIONAL SEARCH REPORT		International application No. PCT/JP01/10115												
A. CLASSIFICATION OF SUBJECT MATTER Int.Cl' C07H15/203, A61K31/7034, A61P3/10, 3/04, 43/00														
According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl' C07H15/203, A61K31/7034														
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched														
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) REGISTRY (STN), CAPLUS (STN), CAOLD (STN)														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category*</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">PX</td> <td style="padding: 2px;">WO 01/74834 A1 (Bristol-Myers Squibb Company), 11 October, 2001 (11.10.2001), (Family: none) Full text</td> <td style="padding: 2px;">1-4, 6-10, 12, 13</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">EP 598359 A1 (Tanabe Seiyaku Co., Ltd.), 24 May, 1994 (24.05.1994), & JP 6-199886 A & JP 6-298790 A & JP 6-305971 A & US 5424406 A & US 5731292 A & CA 2102591 A & TW 283643 A & SG 54120 A1 & DE 69328856 E & ES 2149186 T3 & KR 211438 B1</td> <td style="padding: 2px;">1-10, 12</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">JP 9-241128 A (Nippon Paint Co., Ltd.), 16 September, 1997 (16.09.1997). (Family: none)</td> <td style="padding: 2px;">1-6, 13</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	PX	WO 01/74834 A1 (Bristol-Myers Squibb Company), 11 October, 2001 (11.10.2001), (Family: none) Full text	1-4, 6-10, 12, 13	A	EP 598359 A1 (Tanabe Seiyaku Co., Ltd.), 24 May, 1994 (24.05.1994), & JP 6-199886 A & JP 6-298790 A & JP 6-305971 A & US 5424406 A & US 5731292 A & CA 2102591 A & TW 283643 A & SG 54120 A1 & DE 69328856 E & ES 2149186 T3 & KR 211438 B1	1-10, 12	A	JP 9-241128 A (Nippon Paint Co., Ltd.), 16 September, 1997 (16.09.1997). (Family: none)	1-6, 13
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A	JP 9-241128 A (Nippon Paint Co., Ltd.), 16 September, 1997 (16.09.1997). (Family: none)	1-6, 13												
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "B" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search 24 January, 2002 (24.01.02)	Date of mailing of the international search report 05 February, 2002 (05.02.02)													
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer													
Facsimile No.	Telephone No.													

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/10115

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5232946 A (Dr. Karl Thomae GmbH), 03 August, 1993 (03.08.1993), & JP 3-503405 A & DE 3718638 A1 & WO 90/06299 A1 & AU 8826115 A1 & EP 375791 A1 & EP 400011 A1 & AT 100792 E & CA 1325210 A1 & DK 9001619 A	1-10, 12, 13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/10115

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
<p>1. <input checked="" type="checkbox"/> Claims Nos.: 11 because they relate to subject matter not required to be searched by this Authority, namely: Claim 11 pertains to methods for treatment of the human body by therapy.</p> <p>2. <input type="checkbox"/> Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:</p> <p>3. <input type="checkbox"/> Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</p>	
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
This International Searching Authority found multiple inventions in this international application, as follows:	
<p>1. <input type="checkbox"/> As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.</p> <p>2. <input type="checkbox"/> As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.</p> <p>3. <input type="checkbox"/> As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:</p> <p>4. <input type="checkbox"/> No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:</p>	
<p>Remark on Protest <input type="checkbox"/> The additional search fees were accompanied by the applicant's protest. <input type="checkbox"/> No protest accompanied the payment of additional search fees.</p>	

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)